FORMULATION DEVELOPMENT AND EVALUATION OF FENOFIBRATE CAPSULES

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IN

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CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION DEVELOPMENT AND EVALUATION OF FENOFIBRATE CAPSULE**" submitted by **Mr**. **M. RAMVIKAS** to The Tamilnadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment for the award of Master of Pharmacy in Pharmaceutics at K.M. College of Pharmacy, Madurai, is a bonafide work carried out by him under my guidance and supervision during the academic year 2011-2012.

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DEDICATED TO MY PARENTS

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M.Ramvikas

ABBREVATIONS

BCS	Biopharmaceutics classification system
GIT	Gastrointestinal tract
US-FDA	United states- Food & Drug administration
L	Litre
ml	millilitre
hr	hour
min	minute
sec	second
gm	gram
mg	milligram
ADME	Absorption, Distribution, Metabolism & Excretion
nm	nanometre
mm	millimetre
µm	micrometre
W/W	weight/weight
W/V	weight/volume
µg/ml	microgram/milllilitre
g/cc	gram/cubiccentimetre
m^2/g	Square metre/ gram
#	mesh size
^0c	Degree celsius
RPM	Rotation per minute
%	Percentage
API	Active pharmaceutical ingredients
ICH	International conference on harmonization
USP	United states Pharmacopoeia

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7. RESULTS AND DISCUSSION

The present study was undertaken to formulate Micronized Fenofibrate capsules. Fenofibrate belongs to BCS class-II drugs, having low solubility profile hence to improve the solubility of drug, different approaches were carried out in the formulations like Micronization, Addition of surfactant, optimization of binder with its concentration and Requirement of granulating fluid in the formulation.

The granules prepared in the present study by Wet granulation method have advantages over those prepared by other methods in terms of time and energy consumption, thus making it possible to formulate capsules at a lower cost. Due to their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery.

The study involved Micronization of drug, pre-formulation studies, Granulation steps, formulation and processing development along with evaluation of the capsules.

7.1 MICRONIZATION OF DRUG:

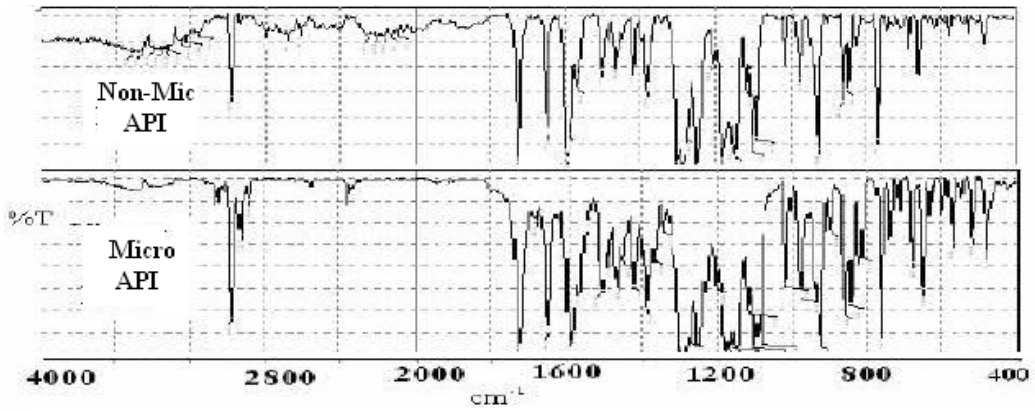
Before going to pre-formulation studies, Fenofibrate drug was micronized from 15µ to 7µ using Jet milling at 7 to 8 bar atmospheric pressure by three repeated cycles. The evaluated parameters are described in Pre-formulation study.

7.2 PRE-FORMULATION STUDIES:

7.2.1 FT - INFRA RED SPECTROSCOPIC STUDIES:

By using FT IR technique, Non-Micronized and Micronized forms of API were identified by the frequency of the obtained peaks. The interpretations of the infra red spectrum of the drug are as follows.

Fig.8 FT-IR Spectrum of Non-micronised and Micronised drug



Specific fenofibrate peaks are observed at 2990, 1740, 1660 and 1600cm^{-1} and observed same in micronized formulation.

7.2.2 DRUG-EXCIPIENT COMPATIBILITY STUDY:

The Micronized fenofibrate was subjected to drug-excipients compatibility study with excipients like polyplasdone, microcrystalline cellulose, croscarmellose sodium, Poly vinyl pyrrolidine, starch, sodium lauryl sulfate, Aerosil, talc and magnesium stearate. The mixtures shown have no color change.

7.2.3 PHYSICAL PARAMETERS:

- The angle of repose for pure micronized drug was very less and hence the poor flow of the pure drug was exhibited. Also the compressibility index of the pure drug was found to be high, confirming that the drug has poor flow properties and compressibility.
- Good flow of powders / granules is essential for capsule filling because the compressibility & flow properties of the drugs likely to influence the compression process in the preparation of capsules. In view of this the formulation were prepared by wet granulation technique to improve the flow as well as compressibility.
- Loss on drying for micronized fenofibrate also show better results.

Table:4 Physical parameter data for the pure drug

Density Parameters	Non-micronised	After Ist cycle	After2ndcycle	After3rdcycle
Bulk density (g/cc)	0.178	0.176	0.173	0.172
Tapped density (g/cc)	0.446	0.452	0.464	0.475
Compressibility Index (%)	56.15	58.62	61.32	64.04
Hausner ratio	2.228	2.531	2.645	2.778
Angle of repose (θ)	$12^0$34''	$10^0$54''	$10^0$14''	$10^0$24''
Loss on Drying(%)	0.415	0.408	0.398	0.406

*Values mentioned are average of 3 determinations.

- When the Non-micronized and micronized drug was subjected for Aqueous solubility studies in which Non-micronized drug shows 0.25mg/ml having poor solubility as well as micronized drug shows 0.74mg/ml having improved solubility.

7.2.4. ANALYTICAL PROPERTIES:

Concentration (µg/ml)	Absorbance
2	0.099
4	0.199
6	0.301
8	0.400
10	0.497
12	0.598
14	0.701
16	0.803

From the standard calibration curve of drug it was concluded that drug obeys Beer-Lamberts law in concentration range of 2-16mcg/ml. Standard calibration graph and table were given below.

Table:5 Standard calibration curve data for Fenofibrate API

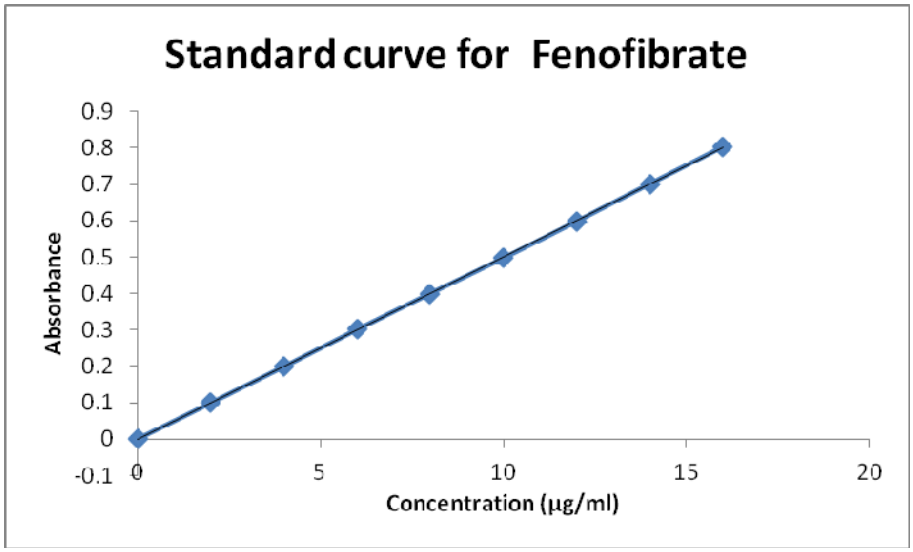


Fig.9 Calibration Graph Of Fenofibrate

The linear equation were obtained as

$$Y=0.0501X - 0.0011, R^2=0.9995$$

Correlation coefficient values indicated the linear correlation between concentration and absorbance.

7.2.5. CRYSTAL PROPERTIES:

- When the fenofibrate subjected to three cycling process results in decrease in particle size from 14µm to 7µm and also increases in surface area after three cycling process. There is no change in melting point of fenofibrate after micronization.

Table:6 Particle Size Parameters

Particle Parameters		**Non-micronised**	**After Ist cycle**	**After2ndcycle**	**After3rdcycle**
Particle size(µm)	D (0.10)	1.323	0.946	0.871	0.800
	D (0.50)	7.004	5.141	4.451	3.925
	D (0.90)	13.713	10.362	9.517	7.832
Surface area (m^2/g)		0.76	1.12	1.48	1.94
Melting point		80	79	81	80

- The X-Ray diffraction pattern of the API sample and reference were overlapping with identical 2θ and d-spacing values. This confirms the identification of the API.
- The X-Ray diffraction pattern of micronized and Non-micronized API exhibited sharp, highly intense and less diffused peaks indicates the crystallinity nature of drug. The graphs are shown in Figure below.

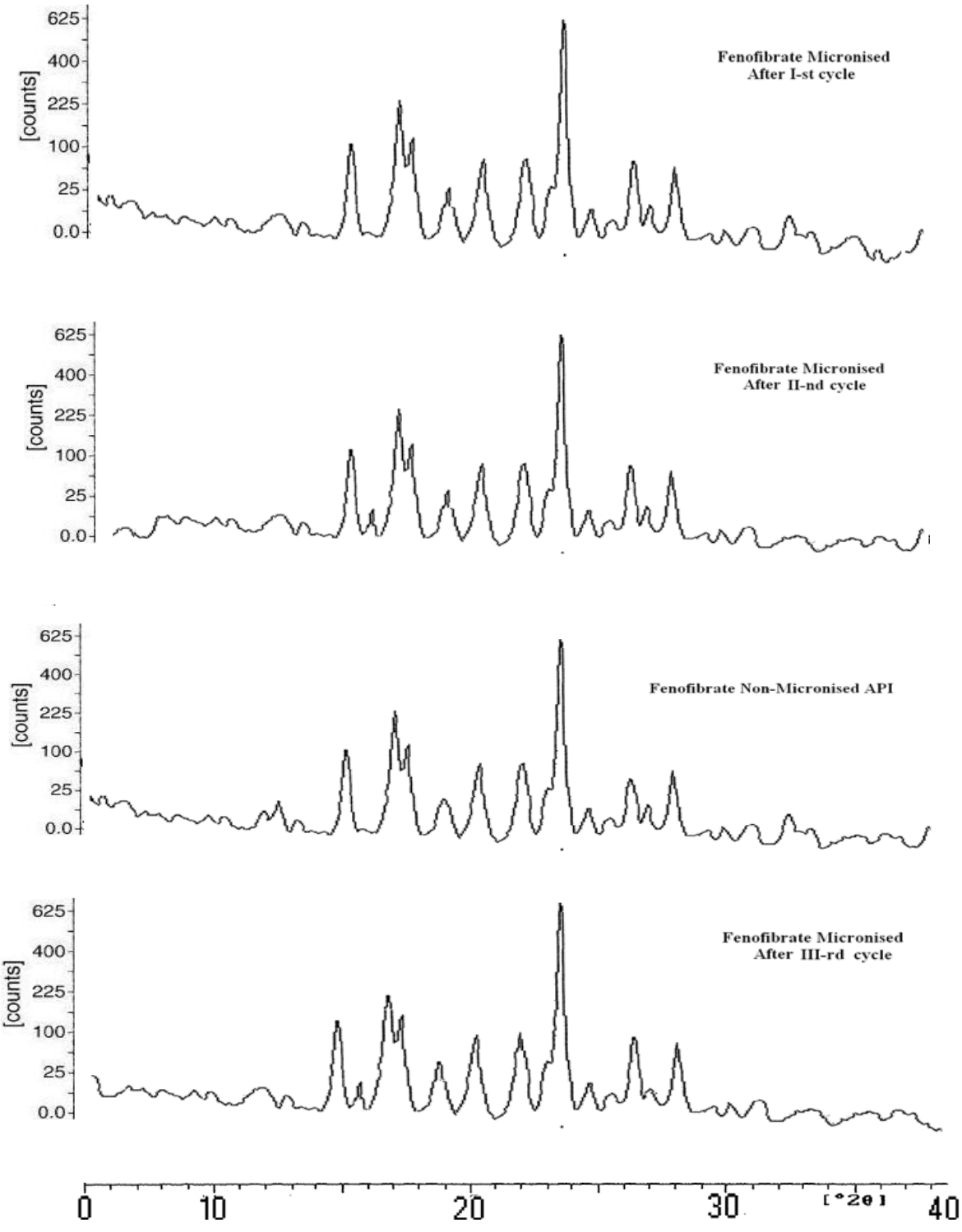


Fig.10 XRD Pattern of Fenofibrate

7.3.1. FORMULATION SHEET

Product: Fenofibrate capsules	Batch size: 500 capsules
Batch No: F01	Date: xx/yy/zz

DISPENSING:

Ingredients	Grade	Qty/unit in mg	Qty/ batch in gm
1.Fenofibrate	Micronised	200.0	100.0
2.Micro crystalline cellulose	Avicel pH-101	33.5	16.75
3.Starch	Unipure F	12.0	6.0
4.Cross povidone	XL-10	16.5	8.25
5.Poly Vinyl Pyrollidine	K-25	12.0	6.0
6.Crosscarmellose Sodium	Ac-Di-Sol	12.0	6.0
7.Sodium lauryl sulfate	---	9.0	4.5
8.Collidal silicon dioxide	Aerosil 200	1.0	0.5
9.Talc	---	1.0	0.5
10.Magnesium stearate	---	3.0	1.5
11.Purified water	---	q.s	q.s

GRANULATION:

Equipment used: Rapid mixer granulator	Volume: 8L	Type: Wet method

A) Sifting:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.Fenofibrate	100gm	40#	4.Cross povidone XL-10	6.0gm	40#
2.MCC pH-101	13.50gm	40#	5.Ac-Di-Sol	6.0gm	40#
3.Unipure starch	6.0gm	40#	6.Sodium lauryl sulfate	4.5gm	40#

B) Dry mix:

Sequence of addition: Add 1+2+3+4		
Mixer blade : ON	Amperage: Slow	Time: 10 min
Chopper blade: OFF	Amperage: ---	Time: ---

C) **Binder preparation**:

Add 6gm of PVP K-25 in 45gm of purified water and stir well with mechanical stirrer for 45 minutes.

Total Water quantity: 42.5gm + 2.5gm	Binder concentration(%w/w): 4.0%

D) Wet granulation:

Process	Mixer blade	Chopper blade	Amperage	Time
Binder addition	ON	OFF	Slow	1 min 30 sec
Extra water adiition	ON	OFF	Slow	30 sec
After binder addition	ON	ON	Slow	5 min

E) Wet sieving

Equipment: Hand mill	Screen size: 30#

DRYING:

Equipment: Fluidized bed dryer	Temperature: 55^0c	Time: 2hrs
LOD: NMT 2.0% (50^0c for 5min)		

A) Dry sieving:

Equipment: Vibratory siever	Sieve no: 30#	
Total Qty : 138.95	Qty retained: 50.48	Qty passed: 88.47

EXTRA-GRANULATION:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.MCC pH-101	3.18gm	40#	3.Talc	0.48gm	40#
2.Aerosil 200	0.48gm	40#	4.Cross povidone XL-10	2.20gm	40#

Sequence of addition: Dried granules + Above meshed ingredients		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 20mins

LUBRICATION:

Lubricator: Magnesium stearate	Qty taken: 1.45gm	Mesh size: 60#
Sequence of addition: Addition of lubricator to extra granulated product		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 5mins

Final weight of batch: 146.7gm	Percentage yield: 97.8%

CAPSULE FILLING:

A) Capsule description:

Capsule Size: '1'	Colour		Imprinting	
	Body: Green	Cap: Green	Body: G	Cap: G302

Target wt: 300mg/capsule	Wt. of empty capsule: 76 mg
Total wt. of granules used: 146.7gm	No. of capsules required: 500

B) Observation

Flow on plate: Good	Pressing required: Two turns
Fill Pressure: Normal	

No. of capsules filled: 490

7.3.2. FORMULATION SHEET

Product: Fenofibrate capsules	Batch size: 500 capsules
Batch No: F02	Date: xx/yy/zz

DISPENSING:

Ingredients	Grade	Qty/unit in mg	Qty/ batch in gm
1.Fenofibrate	Micronised	200.0	100.0
2.Micro crystalline cellulose	Avicel pH-101	27.5	13.75
3.Starch	Unipure F	12.0	6.0
4.Cross povidone	XL-10	16.5	8.25
5.Poly Vinyl Pyrollidine	K-25	18.0	9.0
6.Crosscarmellose Sodium	Ac-Di-Sol	12.0	6.0
7.Sodium lauryl sulfate	---	9.0	4.5
8.Collidal silicon dioxide	Aerosil 200	1.0	0.5
9.Talc	---	1.0	0.5
10.Magnesium stearate	---	3.0	1.5
11.Purified water	---	q.s	q.s

GRANULATION:

Equipment used: Rapid mixer granulator	Volume: 8L	Type: Wet method

A) Sifting:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.Fenofibrate	100gm	40#	4.Cross povidone XL-10	6.0gm	40#
2.MCC pH-101	10.50gm	40#	5.Ac-Di-Sol	6.0gm	40#
3.Unipure starch	6.0gm	40#	6.Sodium lauryl sulfate	4.5gm	40#

B) Dry mix:

Sequence of addition: Add 1+2+3+4		
Mixer blade : ON	Amperage: Slow	Time: 10 min
Chopper blade: OFF	Amperage: ---	Time: ---

C) **Binder preparation**:

Add 9gm of PVP K-25 in 45gm of purified water and stir well with mechanical stirrer for 45 minutes.

Total Water quantity: 42.5gm + 2.5gm	Binder concentration(%w/w): 6.0%

D) Wet granulation:

Process	Mixer blade	Chopper blade	Amperage	Time
Binder addition	ON	OFF	Slow	1 min 30 sec
Extra water adiition	ON	OFF	Slow	30 sec
After binder addition	ON	ON	Slow	5 min

E) Wet sieving

Equipment: Hand mill	Screen size: 30#

DRYING:

Equipment: Fluidized bed dryer	Temperature: 55^0c	Time: 2hrs
LOD: NMT 2.0% (50^0c for 5min)		

A) Dry sieving:

Equipment: Vibratory siever	Sieve no: 30#	
Total Qty : 139.95	Qty retained: 52.65	Qty passed: 87.3

EXTRA-GRANULATION:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.MCC pH-101	4.95gm	40#	3.Talc	0.49gm	40#
2.Aerosil 200	0.49gm	40#	4.Cross povidone XL-10	2.20gm	40#

Sequence of addition: Dried granules + Above meshed ingredients		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 20mins

LUBRICATION:

Lubricator: Magnesium stearate	Qty taken: 1.475gm	Mesh size: 60#
Sequence of addition: Addition of lubricator to extra granulated product		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 5mins

Final weight of batch: 148.2gm	Percentage yield: 98.8%

CAPSULE FILLING:

A) Capsule description:

Capsule Size: '1'	Colour		Imprinting	
	Body: Green	Cap: Green	Body: G	Cap: G302

Target wt: 300mg/capsule	Wt. of empty capsule: 76 mg
Total wt. of granules used: 148.2gm	No. of capsules required: 500

B) Observation

Flow on plate: Good	Pressing required: Two turns
Fill Pressure: Normal	

No. of capsules filled: 494

7.3.3. FORMULATION SHEET

Product: Fenofibrate capsules	Batch size: 500 capsules
Batch No: F03	Date: xx/yy/zz

DISPENSING:

Ingredients	Grade	Qty/unit in mg	Qty/ batch in gm
1.Fenofibrate	Micronised	200.0	100.0
2.Micro crystalline cellulose	Avicel pH-101	21.5	10.75
3.Starch	Unipure F	12.0	6.0
4.Cross povidone	XL-10	16.5	8.25
5.Poly Vinyl Pyrollidine	K-25	24.0	12.0
6.Crosscarmellose Sodium	Ac-Di-Sol	12.0	6.0
7.Sodium lauryl sulfate	---	9.0	4.5
8.Collidal silicon dioxide	Aerosil 200	1.0	0.5
9.Talc	---	1.0	0.5
10.Magnesium stearate	---	3.0	1.5
11.Purified water	---	q.s	q.s

GRANULATION:

Equipment used: Rapid mixer granulator	Volume: 10L	Type: Wet method

A) Sifting:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.Fenofibrate	100gm	40#	4.Cross povidone XL-10	6.0gm	40#
2.MCC pH-101	7.50gm	40#	5.Ac-Di-Sol	6.0gm	40#
3.Unipure starch	6.0gm	40#	6.Sodium lauryl sulfate	4.5gm	40#

B) Dry mix:

Sequence of addition: Add 1+2+3+4		
Mixer blade : ON	Amperage: Slow	Time: 10 min
Chopper blade: OFF	Amperage: ---	Time: ---

C) **Binder preparation**:

Add 12gm of PVP K-25 in 45gm of purified water and stir well with mechanical stirrer for 45 minutes.

Total Water quantity: 42.5gm + 2.5gm	Binder concentration(%w/w): 8.0%

D) Wet granulation:

Process	Mixer blade	Chopper blade	Amperage	Time
Binder addition	ON	OFF	Slow	1 min 30 sec
Extra water adiition	ON	OFF	Slow	30 sec
After binder addition	ON	ON	Slow	5 min

E) Wet sieving

Equipment: Hand mill	Screen size: 30#

DRYING:

Equipment: Fluidized bed dryer	Temperature: 55^0c	Time: 2hrs
LOD: NMT 2.0% (50^0c for 5min)		

A) Dry sieving:

Equipment: Vibratory siever	Sieve no: 30#	
Total Qty : 139.20	Qty retained: 57.10	Qty passed: 82.10

EXTRA-GRANULATION:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.MCC pH-101	3.18gm	40#	3.Talc	0.48gm	40#
2.Aerosil 200	0.48gm	40#	4.Cross povidone XL-10	2.20gm	40#

Sequence of addition: Dried granules + Above meshed ingredients		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 20mins

LUBRICATION:

Lubricator: Magnesium stearate	Qty taken: 1.45gm	Mesh size: 60#
Sequence of addition: Addition of lubricator to extra granulated product		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 5mins

Final weight of batch: 147.30gm	Percentage yield: 98.2%

CAPSULE FILLING:

A) Capsule description:

Capsule Size: '1'	Colour		Imprinting	
	Body: Green	Cap: Green	Body: G	Cap: G302

Target wt: 300mg/capsule	Wt. of empty capsule: 76 mg
Total wt. of granules used: 147.3gm	No. of capsules required: 500

B) Observation

Flow on plate: Good	Pressing required: Two turns
Fill Pressure: Normal	

No. of capsules filled: 491

7.3.4. FORMULATION SHEET

Product: Fenofibrate capsules	Batch size: 500 capsules
Batch No: F04	Date: xx/yy/zz

DISPENSING:

Ingredients	Grade	Qty/unit in mg	Qty/ batch in gm
1.Fenofibrate	Micronised	200.0	100.0
2.Micro crystalline cellulose	Avicel pH-101	27.5	13.75
3.Starch	Unipure F	12.0	6.0
4.Cross povidone	XL-10	16.5	8.25
5.Poly Vinyl Pyrollidine	K-25	18.0	9.0
6.Crosscarmellose Sodium	Ac-Di-Sol	12.0	6.0
7.Sodium lauryl sulfate	---	9.0	4.5
8.Collidal silicon dioxide	Aerosil 200	1.0	0.5
9.Talc	---	1.0	0.5
10.Magnesium stearate	---	3.0	1.5
11.Purified water	---	q.s	q.s

GRANULATION:

Equipment used: Rapid mixer granulator	Volume: 8L	Type: Wet method

A) Sifting:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.Fenofibrate	100gm	40#	4.Cross povidone XL-10	6.0gm	40#
2.MCC pH-101	10.50gm	40#	5.Ac-Di-Sol	6.0gm	40#
3.Unipure starch	6.0gm	40#	6.Sodium lauryl sulfate	---	---

B) Dry mix:

Sequence of addition: Add 1+2+3+4		
Mixer blade : ON	Amperage: Slow	Time: 10 min
Chopper blade: OFF	Amperage: ---	Time: ---

C) **Binder preparation**:

Add 9gm of PVP K-25 and 4.5gm of SLS in 45gm of purified water and stir well with mechanical stirrer for 45 minutes.

Total Water quantity: 42.5gm + 2.5gm	Binder concentration(%w/w): 6.0%

D) Wet granulation:

Process	Mixer blade	Chopper blade	Amperage	Time
Binder addition	ON	OFF	Slow	1 min 30 sec
Extra water adiition	ON	OFF	Slow	30 sec
After binder addition	ON	ON	Slow	5 min

E) Wet sieving

Equipment: Hand mill	Screen size: 30#

DRYING:

Equipment: Fluidized bed dryer	Temperature: 55^0c	Time: 2hrs
LOD: NMT 2.0% (50^0c for 5min)		

A) Dry sieving:

Equipment: Vibratory siever	Sieve no: 30#	
Total Qty : 138.75	Qty retained: 52.55	Qty passed: 86.20

EXTRA-GRANULATION:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.MCC pH-101	3.18gm	40#	3.Talc	0.48gm	40#
2.Aerosil 200	0.48gm	40#	4.Cross povidone XL-10	2.20gm	40#

Sequence of addition: Dried granules + Above meshed ingredients		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 20mins

LUBRICATION:

Lubricator: Magnesium stearate	Qty taken: 1.45gm	Mesh size: 60#
Sequence of addition: Addition of lubricator to extra granulated product		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 5mins

Final weight of batch: 145.95gm	Percentage yield: 97.3%

CAPSULE FILLING:

A) Capsule description:

Capsule Size: '1'	Colour		Imprinting	
	Body: Green	Cap: Green	Body: G	Cap: G302

Target wt: 300mg/capsule	Wt. of empty capsule: 76 mg
Total wt. of granules used: 145.95gm	No. of capsules required: 500

B) Observation

Flow on plate: Good	Pressing required: Two turns
Fill Pressure: Normal	

No. of capsules filled: 486

7.3.5. FORMULATION SHEET

Product: Fenofibrate capsules	Batch size: 500 capsules
Batch No: F05	Date: xx/yy/zz

DISPENSING:

Ingredients	Grade	Qty/unit in mg	Qty/ batch in gm
1.Fenofibrate	Micronised	200.0	100.0
2.Micro crystalline cellulose	Avicel pH-101	27.5	13.75
3.Starch	Unipure F	12.0	6.0
4.Cross povidone	XL-10	16.5	8.25
5.Poly Vinyl Pyrollidine	K-25	18.0	9.0
6.Crosscarmellose Sodium	Ac-Di-Sol	12.0	6.0
7.Sodium lauryl sulfate	---	9.0	4.5
8.Collidal silicon dioxide	Aerosil 200	1.0	0.5
9.Talc	---	1.0	0.5
10.Magnesium stearate	---	3.0	1.5
11.Purified water	---	q.s	q.s

GRANULATION:

Equipment used: Rapid mixer granulator	Volume: 8L	Type: Wet method

A) Sifting:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.Fenofibrate	100gm	40#	4.Cross povidone XL-10	6.0gm	40#
2.MCC pH-101	10.50gm	40#	5.Ac-Di-Sol	6.0gm	40#
3.Unipure starch	6.0gm	40#	6.Sodium lauryl sulfate	3.0gm	40#

B) Dry mix:

Sequence of addition: Add 1+2+3+4		
Mixer blade : ON	Amperage: Slow	Time: 10 min
Chopper blade: OFF	Amperage: ---	Time: ---

C) **Binder preparation**:

Add 9gm of PVP K-25 and 1.5gm of SLS in 45gm of purified water and stir well with mechanical stirrer for 45 minutes.

Total Water quantity: 42.5gm + 2.5gm	Binder concentration(%w/w): 6.0%

D) Wet granulation:

Process	Mixer blade	Chopper blade	Amperage	Time
Binder addition	ON	OFF	Slow	1 min 30 sec
Extra water adiition	ON	OFF	Slow	30 sec
After binder addition	ON	ON	Slow	5 min

E) Wet sieving

Equipment: Hand mill	Screen size: 30#	
DRYING:		
Equipment: Fluidized bed dryer	Temperature: 55^0c	Time: 2hrs
LOD: NMT 2.0% (50^0c for 5min)		

A) Dry sieving:

Equipment: Vibratory siever	Sieve no: 30#	
Total Qty : 139.55	Qty retained: 53.35	Qty passed: 86.20

EXTRA-GRANULATION:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.MCC pH-101	4.95gm	40#	3.Talc	0.49gm	40#
2.Aerosil 200	0.49gm	40#	4.Cross povidone XL-10	2.20gm	40#

Sequence of addition: Dried granules + Above meshed ingredients		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 20mins

LUBRICATION:

Lubricator: Magnesium stearate	Qty taken: 1.475gm	Mesh size: 60#
Sequence of addition: Addition of lubricator to extra granulated product		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 5mins

Final weight of batch: 147.60gm	Percentage yield: 98.4%

CAPSULE FILLING:

A) Capsule description:

Capsule Size: '1'	Colour		Imprinting	
	Body: Green	Cap: Green	Body: G	Cap: G302

Target wt: 300mg/capsule	Wt. of empty capsule: 76 mg
Total wt. of granules used: 147.60gm	No. of capsules required: 500

B) Observation

Flow on plate: Good	Pressing required: Two turns
Fill Pressure: Normal	

No. of capsules filled: 492

7.3.6. FORMULATION SHEET

Product: Fenofibrate capsules	Batch size: 500 capsules
Batch No: F06	Date: xx/yy/zz

DISPENSING:

Ingredients	Grade	Qty/unit in mg	Qty/ batch in gm
1.Fenofibrate	Micronised	200.0	100.0
2.Micro crystalline cellulose	Avicel pH-101	27.5	13.75
3.Starch	Unipure F	12.0	6.0
4.Cross povidone	XL-10	16.5	8.25
5.Poly Vinyl Pyrollidine	K-25	18.0	9.0
6.Crosscarmellose Sodium	Ac-Di-Sol	12.0	6.0
7.Sodium lauryl sulfate	---	9.0	4.5
8.Collidal silicon dioxide	Aerosil 200	1.0	0.5
9.Talc	---	1.0	0.5
10.Magnesium stearate	---	3.0	1.5
11.Purified water	---	q.s	q.s

GRANULATION:

Equipment used: Rapid mixer granulator	Volume: 8L	Type: Wet method

A) Sifting:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.Fenofibrate	100gm	40#	4.Cross povidone XL-10	6.0gm	40#
2.MCC pH-101	10.50gm	40#	5.Ac-Di-Sol	6.0gm	40#
3.Unipure starch	6.0gm	40#	6.Sodium lauryl sulfate	1.5gm	40#

B) Dry mix:

Sequence of addition: Add 1+2+3+4		
Mixer blade : ON	Amperage: Slow	Time: 10 min
Chopper blade: OFF	Amperage: ---	Time: ---

C) **Binder preparation**:

Add 9gm of PVP K-25 and 3.0gm of SLS in 45gm of purified water and stir well with mechanical stirrer for 45 minutes.

Total Water quantity: 42.5gm + 2.5gm	Binder concentration(%w/w): 6.0%

D) Wet granulation:

Process	Mixer blade	Chopper blade	Amperage	Time
Binder addition	ON	OFF	Slow	1 min 30 sec
Extra water adiition	ON	OFF	Slow	30 sec
After binder addition	ON	ON	Slow	5 min

E) Wet sieving

Equipment: Hand mill	Screen size: 30#

DRYING:

Equipment: Fluidized bed dryer	Temperature: 55^0c	Time: 2hrs
LOD: NMT 2.0% (50^0c for 5min)		

A) Dry sieving:

Equipment: Vibratory siever	Sieve no: 30#	
Total Qty : 139.35	Qty retained: 53.25	Qty passed: 86.10

EXTRA-GRANULATION:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.MCC pH-101	4.95gm	40#	3.Talc	0.49gm	40#
2.Aerosil 200	0.49gm	40#	4.Cross povidone XL-10	2.20gm	40#
Sequence of addition: Dried granules + Above meshed ingredients					
Equipment: Octagonal blender	Rotation per minute: 15		Time: 20mins		

LUBRICATION:

Lubricator: Magnesium stearate	Qty taken: 1.475gm	Mesh size: 60#
Sequence of addition: Addition of lubricator to extra granulated product		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 5mins

Final weight of batch: 147.45gm	Percentage yield: 98.3%

CAPSULE FILLING:

A) Capsule description:

Capsule Size: '1'	Colour		Imprinting	
	Body: Green	Cap: Green	Body: G	Cap: G302
Target wt: 300mg/capsule			Wt. of empty capsule: 76 mg	
Total wt. of granules used: 147.60gm			No. of capsules required: 500	

B) Observation

Flow on plate: Good	Pressing required: Two turns
Fill Pressure: Normal	
No. of capsules filled: 492	

7.3.7. FORMULATION SHEET

Product: Fenofibrate capsules	Batch size: 500 capsules
Batch No: F07	Date: xx/yy/zz

DISPENSING:

Ingredients	Grade	Qty/unit in mg	Qty/ batch in gm
1.Fenofibrate	Micronised	200.0	100.0
2.Micro crystalline cellulose	Avicel pH-101	27.5	13.75
3.Starch	Unipure F	12.0	6.0
4.Cross povidone	XL-10	16.5	8.25
5.Poly Vinyl Pyrollidine	K-25	18.0	9.0
6.Crosscarmellose Sodium	Ac-Di-Sol	12.0	6.0
7.Sodium lauryl sulfate	---	9.0	4.5
8.Collidal silicon dioxide	Aerosil 200	1.0	0.5
9.Talc	---	1.0	0.5
10.Magnesium stearate	---	3.0	1.5
11.Purified water	---	q.s	q.s

GRANULATION:

Equipment used: Rapid mixer granulator	Volume: 8L	Type: Wet method

A) Sifting:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.Fenofibrate	100gm	40#	4.Cross povidone XL-10	6.0gm	40#
2.MCC pH-101	10.50gm	40#	5.Ac-Di-Sol	6.0gm	40#
3.Unipure starch	6.0gm	40#	6.Sodium lauryl sulfate	2.25gm	40#

B) Dry mix:

Sequence of addition: Add 1+2+3+4		
Mixer blade : ON	Amperage: Slow	Time: 10 min
Chopper blade: OFF	Amperage: ---	Time: ---

C) **Binder preparation**:

Add 9gm of PVP K-25 and 2.25gm of SLS in 45gm of purified water and stir well with mechanical stirrer for 45 minutes.

Total Water quantity: 42.5gm + 2.5gm	Binder concentration(%w/w): 6.0%

D) Wet granulation:

Process	Mixer blade	Chopper blade	Amperage	Time
Binder addition	ON	OFF	Slow	1 min 30 sec
Extra water adiition	ON	OFF	Slow	30 sec
After binder addition	ON	ON	Slow	5 min

E) Wet sieving

Equipment: Hand mill	Screen size: 30#

DRYING:

Equipment: Fluidized bed dryer	Temperature: 55^0c	Time: 2hrs
LOD: NMT 2.0% (50^0c for 5min)		

A) Dry sieving:

Equipment: Vibratory siever	Sieve no: 30#	
Total Qty : 139.15	Qty retained: 52.85	Qty passed: 86.30

EXTRA-GRANULATION:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.MCC pH-101	4.95gm	40#	3.Talc	0.49gm	40#
2.Aerosil 200	0.49gm	40#	4.Cross povidone XL-10	2.20gm	40#

Sequence of addition: Dried granules + Above meshed ingredients		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 20mins

LUBRICATION:

Lubricator: Magnesium stearate	Qty taken: 1.475gm	Mesh size: 60#
Sequence of addition: Addition of lubricator to extra granulated product		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 5mins

Final weight of batch: 147.15gm	Percentage yield: 98.1%

CAPSULE FILLING:

A) Capsule description:

Capsule Size: '1'	Colour		Imprinting	
	Body: Green	Cap: Green	Body: G	Cap: G302

Target wt: 300mg/capsule	Wt. of empty capsule: 76 mg
Total wt. of granules used: 147.60gm	No. of capsules required: 500

B) Observation

Flow on plate: Good	Pressing required: Two turns
Fill Pressure: Normal	

No. of capsules filled: 491

7.3.8. FORMULATION SHEET

Product: Fenofibrate capsules	Batch size: 500 capsules
Batch No: F08	Date: xx/yy/zz

DISPENSING:

Ingredients	Grade	Qty/unit in mg	Qty/ batch in gm
1.Fenofibrate	Micronised	200.0	100.0
2.Micro crystalline cellulose	Avicel pH-101	27.5	13.75
3.Starch	Unipure F	12.0	6.0
4.Cross povidone	XL-10	16.5	8.25
5.Poly Vinyl Pyrollidine	K-25	18.0	9.0
6.Crosscarmellose Sodium	Ac-Di-Sol	12.0	6.0
7.Sodium lauryl sulfate	---	9.0	4.5
8.Collidal silicon dioxide	Aerosil 200	1.0	0.5
9.Talc	---	1.0	0.5
10.Magnesium stearate	---	3.0	1.5
11.Purified water	---	q.s	q.s

GRANULATION:

Equipment used: Rapid mixer granulator	Volume: 8L	Type: Wet method

A) Sifting:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.Fenofibrate	100gm	40#	4.Cross povidone XL-10	6.0gm	40#
2.MCC pH-101	10.50gm	40#	5.Ac-Di-Sol	6.0gm	40#
3.Unipure starch	6.0gm	40#	6.Sodium lauryl sulfate	1.5gm	40#

B) Dry mix:

Sequence of addition: Add 1+2+3+4		
Mixer blade : ON	Amperage: Slow	Time: 10 min
Chopper blade: OFF	Amperage: ---	Time: ---

C) **Binder preparation**:

Add 9gm of PVP K-25 and 3.0gm of SLS in 50gm of purified water and stir well with mechanical stirrer for 45 minutes.

Total Water quantity: 47.5gm + 2.5gm	Binder concentration(%w/w): 6.0%

D) Wet granulation:

Process	Mixer blade	Chopper blade	Amperage	Time
Binder addition	ON	OFF	Slow	1 min 30 sec
Extra water adiition	ON	OFF	Slow	30 sec
After binder addition	ON	ON	Slow	5 min

E) Wet sieving

Equipment: Hand mill	Screen size: 30#

DRYING:

Equipment: Fluidized bed dryer	Temperature: 55^0c	Time: 2hrs
LOD: NMT 2.0% (50^0c for 5min)		

A) Dry sieving:

Equipment: Vibratory siever	Sieve no: 30#	
Total Qty : 138.85	Qty retained: 53.25	Qty passed: 85.60

EXTRA-GRANULATION:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.MCC pH-101	3.18gm	40#	3.Talc	0.48gm	40#
2.Aerosil 200	0.48gm	40#	4.Cross povidone XL-10	2.20gm	40#

Sequence of addition: Dried granules + Above meshed ingredients		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 20mins

LUBRICATION:

Lubricator: Magnesium stearate	Qty taken: 1.45gm	Mesh size: 60#
Sequence of addition: Addition of lubricator to extra granulated product		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 5mins

Final weight of batch: 146.40gm	Percentage yield: 97.6%

CAPSULE FILLING:

A) Capsule description:

Capsule Size: '1'	Colour		Imprinting	
	Body: Green	Cap: Green	Body: G	Cap: G302

Target wt: 300mg/capsule	Wt. of empty capsule: 76 mg
Total wt. of granules used: 146.40gm	No. of capsules required: 500

B) Observation

Flow on plate: Good	Pressing required: Two turns
Fill Pressure: Normal	

No. of capsules filled: 488

7.3.9. FORMULATION SHEET

Product: Fenofibrate capsules	Batch size: 500 capsules
Batch No: F09	Date: xx/yy/zz

DISPENSING:

Ingredients	Grade	Qty/unit in mg	Qty/ batch in gm
1.Fenofibrate	Micronised	200.0	100.0
2.Micro crystalline cellulose	Avicel pH-101	27.5	13.75
3.Starch	Unipure F	12.0	6.0
4.Cross povidone	XL-10	16.5	8.25
5.Poly Vinyl Pyrollidine	K-25	18.0	9.0
6.Crosscarmellose Sodium	Ac-Di-Sol	12.0	6.0
7.Sodium lauryl sulfate	---	9.0	4.5
8.Collidal silicon dioxide	Aerosil 200	1.0	0.5
9.Talc	---	1.0	0.5
10.Magnesium stearate	---	3.0	1.5
11.Purified water	---	q.s	q.s

GRANULATION:

Equipment used: Rapid mixer granulator	Volume: 8L	Type: Wet method

A) Sifting:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.Fenofibrate	100gm	40#	4.Cross povidone XL-10	6.0gm	40#
2.MCC pH-101	10.50gm	40#	5.Ac-Di-Sol	6.0gm	40#
3.Unipure starch	6.0gm	40#	6.Sodium lauryl sulfate	1.5gm	40#

B) Dry mix:

Sequence of addition: Add 1+2+3+4		
Mixer blade : ON	Amperage: Slow	Time: 10 min
Chopper blade: OFF	Amperage: ---	Time: ---

C) **Binder preparation**:

Add 9gm of PVP K-25 and 3.0gm of SLS in 40gm of purified water and stir well with mechanical stirrer for 45 minutes.

Total Water quantity: 37.5gm + 2.5gm	Binder concentration(%w/w): 6.0%

D) Wet granulation:

Process	Mixer blade	Chopper blade	Amperage	Time
Binder addition	ON	OFF	Slow	1 min 30 sec
Extra water adiition	ON	OFF	Slow	30 sec
After binder addition	ON	ON	Slow	5 min

E) Wet sieving

Equipment: Hand mill	Screen size: 30#

DRYING:

Equipment: Fluidized bed dryer	Temperature: 55^0c	Time: 2hrs
LOD: NMT 2.0% (50^0c for 5min)		

A) Dry sieving:

Equipment: Vibratory siever	Sieve no: 30#	
Total Qty : 139.25	Qty retained: 53.85	Qty passed: 85.40

EXTRA-GRANULATION:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.MCC pH-101	4.95gm	40#	3.Talc	0.49gm	40#
2.Aerosil 200	0.49gm	40#	4.Cross povidone XL-10	2.20gm	40#

Sequence of addition: Dried granules + Above meshed ingredients		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 20mins

LUBRICATION:

Lubricator: Magnesium stearate	Qty taken: 1.475gm	Mesh size: 60#
Sequence of addition: Addition of lubricator to extra granulated product		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 5mins

Final weight of batch: 147.38gm	Percentage yield: 98.25%

CAPSULE FILLING:

A) Capsule description:

Capsule Size: '1'	Colour		Imprinting	
	Body: Green	Cap: Green	Body: G	Cap: G302

Target wt: 300mg/capsule	Wt. of empty capsule: 76 mg
Total wt. of granules used: 147.60gm	No. of capsules required: 500

B) Observation

Flow on plate: Good	Pressing required: Two turns
Fill Pressure: Normal	

No. of capsules filled: 492

7.3.10. FORMULATION SHEET

Product: Fenofibrate capsules	Batch size: 500 capsules
Batch No: F10	Date: xx/yy/zz

DISPENSING:

Ingredients	Grade	Qty/unit in mg	Qty/ batch in gm
1.Fenofibrate	Micronised	200.0	100.0
2.Micro crystalline cellulose	Avicel pH-101	27.5	13.75
3.Starch	Unipure F	12.0	6.0
4.Cross povidone	XL-10	16.5	8.25
5.Poly Vinyl Pyrollidine	K-25	18.0	9.0
6.Crosscarmellose Sodium	Ac-Di-Sol	12.0	6.0
7.Sodium lauryl sulfate	---	9.0	4.5
8.Collidal silicon dioxide	Aerosil 200	1.0	0.5
9.Talc	---	1.0	0.5
10.Magnesium stearate	---	3.0	1.5
11.Purified water	---	q.s	q.s

GRANULATION:

Equipment used: Rapid mixer granulator	Volume: 8L	Type: Wet method

A) Sifting:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.Fenofibrate	100gm	40#	4.Cross povidone XL-10	6.0gm	40#
2.MCC pH-101	10.50gm	40#	5.Ac-Di-Sol	6.0gm	40#
3.Unipure starch	6.0gm	40#	6.Sodium lauryl sulfate	1.5gm	40#

B) Dry mix:

Sequence of addition: Add 1+2+3+4		
Mixer blade : ON	Amperage: Slow	Time: 10 min
Chopper blade: OFF	Amperage: ---	Time: ---

C) **Binder preparation**:

Add 9gm of PVP K-25 and 3.0gm of SLS in 35gm of purified water and stir well with mechanical stirrer for 45 minutes.

Total Water quantity: 32.5gm + 2.5gm	Binder concentration(%w/w): 6.0%

D) Wet granulation:

Process	Mixer blade	Chopper blade	Amperage	Time
Binder addition	ON	OFF	Slow	1 min 30 sec
Extra water adiition	ON	OFF	Slow	30 sec
After binder addition	ON	ON	Slow	5 min

E) Wet sieving

Equipment: Hand mill	Screen size: 30#	
DRYING:		
Equipment: Fluidized bed dryer	Temperature: 55^0c	Time: 2hrs
LOD: NMT 2.0% (50^0c for 5min)		

A) Dry sieving:

Equipment: Vibratory siever	Sieve no: 30#	
Total Qty : 139.65	Qty retained: 54.35	Qty passed: 85.30

EXTRA-GRANULATION:

Ingredients	Qty taken	Mesh size	Ingredients	Qty taken	Mesh size
1.MCC pH-101	4.95gm	40#	3.Talc	0.49gm	40#
2.Aerosil 200	0.49gm	40#	4.Cross povidone XL-10	2.20gm	40#

Sequence of addition: Dried granules + Above meshed ingredients		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 20mins

LUBRICATION:

Lubricator: Magnesium stearate	Qty taken: 1.475gm	Mesh size: 60#
Sequence of addition: Addition of lubricator to extra granulated product		
Equipment: Octagonal blender	Rotation per minute: 15	Time: 5mins

Final weight of batch: 147.75gm	Percentage yield: 98.5%

CAPSULE FILLING:

A) Capsule description:

Capsule Size: '1'	Colour		Imprinting	
	Body: Green	Cap: Green	Body: G	Cap: G302

Target wt: 300mg/capsule	Wt. of empty capsule: 76 mg
Total wt. of granules used: 147.60gm	No. of capsules required: 500

B) Observation

Flow on plate: Good	Pressing required: Two turns
Fill Pressure: Normal	
No. of capsules filled: 493	

7.4. EVALUATION OF GRANULES:

7.4.1 PHYSICAL PARAMETERS:

The prepared granules of the formulations were evaluated for the parameters like bulk density, tap density, compressibility index, hausner ratio, angle of repose and loss on drying.

- After granulation, angle of repose was improved.
- Hausner ratio was found to be 1.2 (or) less than 1.2, shows good flow.
- Carr's index was found to be in the range of 11 – 16, proves excellent flow property.
- All these values indicated that the granules have good flow property and hence the granulation process has improved the flow property.
- Loss on drying also within the limit of 2.0%.

Table: 7 Physical Parameters of lubricated blend

Formulation code	Angle of Repose (^{0})	Loss on drying	Bulk density	Tapped density	Hausner ratio	Carr's Index
F_1	25.64 ± 0.762	1.21 ± 0.098	0.350 ± 0.011	0.420 ± 0.002	1.2 ± 0.004	16.6 ± 0.170
F_2	25.56 ± 0.671	1.10 ± 0.085	0.361 ± 0.010	0.430 ± 0.005	1.19 ± 0.002	16.2 ± 0.180
F_3	26.42 ± 0.397	1.12 ± 0.089	0.370 ± 0.012	0.440 ± 0.004	1.18 ± 0.001	15.9 ± 0.181
F_4	25.43 ± 0.754	1.13 ± 0.095	0.350 ± 0.011	0.410 ± 0.006	1.17 ± 0.003	14.63 ± 0.168
F_5	26.42 ± 0.397	1.10 ± 0.095	0.380 ± 0.012	0.450 ± 0.004	1.20 ± 0.002	15.5 ± 0.171
F_6	26.03 ± 0.590	1.11 ± 0.086	0.356 ± 0.011	0.421 ± 0.005	1.18 ± 0.002	15.43 ± 0.065
F_7	26.32 ± 0.310	1.15 ± 0.094	0.361 ± 0.021	0.432 ± 0.002	1.19 ± 0.003	16.43 ± 0.162
F_8	25.98 ± 0.420	1.21 ± 0.098	0.371 ± 0.010	0.412 ± 0.003	1.17 ± 0.004	14.80 ± 0.152
F_9	25.43 ± 0.754	1.15 ± 0.096	0.412 ± 0.012	0.475 ± 0.06	1.15 ± 0.002	15.29 ± 0.181
F_{10}	25.64 ± 0.953	1.20 ± 0.098	0.361 ± 0.020	0.442 ± 0.003	1.19 ± 0.003	16.07 ± 0.101

***Values mentioned are average of 3 determinations**

7.4.2 PARTICLE SIZE DISTRIBUTION ANALYSIS:

Above 50% of the particle passes through 100mesh size and also less than 0.40% of particles retained on 30 mesh size, results in particles having good flow property as well as forms a good compressibility index. When the graph is plotted between mesh size Vs percentage of particles retained on each mesh gives dumb-bell shape curve. The data are given in table-8.

7.4.3. RELATED SUBSTANCES:

As per ICH as well as USP limit for total impurity of both known and unknown is not more than 1.0%. Related substances were carried out by using gas chromatography technique. Related substance value for different formulation was under the ICH limits specified in table-8.

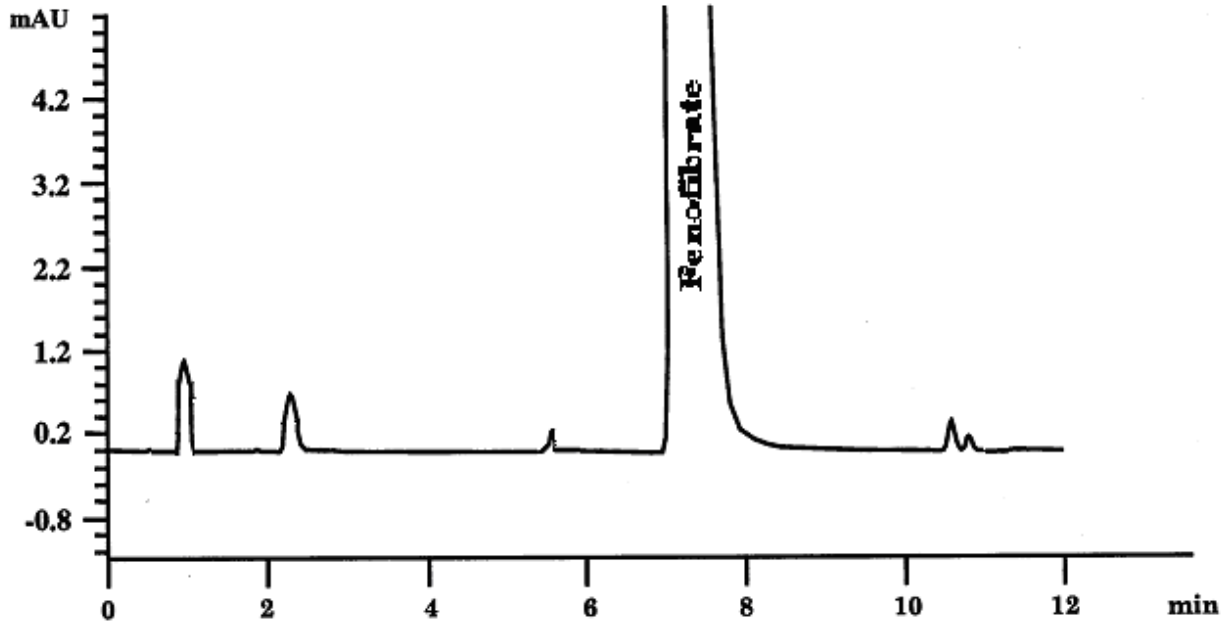


Fig.11 HPLC Spectrum of Fenofibrate with other Related substances

Table:8 Different parameters of lubricated blend

Formulation code	Particle size distribution analysis (%)						Related substance (%)
	30#	40#	60#	80#	100#	Base	
F_1	2.64	15.64	11.36	17.16	12.12	40.92	0.43
F_2	2.04	14.43	12.35	16.16	13.24	41.53	0.53
F_3	1.84	16.44	11.04	17.48	18.22	34.82	0.51
F_4	3.52	16.16	14.40	13.60	9.44	42.28	0.43
F_5	3.05	15.36	15.47	13.80	11.52	40.20	0.46
F_6	3.61	16.15	14.13	13.87	10.53	41.09	0.48
F_7	2.59	16.62	12.37	15.62	11.14	40.18	0.42
F_8	0.52	11.44	5.28	3.10	21.78	57.78	0.47
F_9	0.51	10.24	6.49	3.71	23.17	55.78	0.46
F_{10}	0.52	9.34	6.33	4.15	22.90	56.66	0.42

7.4. EVALUATION OF CAPSULES:

- The weight variation test was carried out for the capsules, shows within the range of 370mg to 380mg for individual capsule and the weight variation within 1 to 3%. It passes the test as per USP limit. The data was compiled in table-9.

- When the Cap lock length was determined for the capsules shows within the range of 19.0 to 19.5mm. The observed values are recorded in table-9.

- The content uniformity test was carried out for all the formulations, shows results within the range of 95% to 105% as per ICH. The observed values are given in table-9.

Table: 9 Evaluation parameters of capsules

Formulation Code	Weight variation (%)	Cap lock length (mm)	Content uniformity (%)
F_1	2.7 ± 0.062	19.2 ± 0.011	97.6 ± 0.701
F_2	2.3 ± 0.17	19.1 ± 0.010	99.2 ± 0.180
F_3	2.2 ± 0.39	19.0 ± 0.012	98.9 ± 0.181
F_4	2.6 ± 0.07	19.3 ± 0.011	97.6 ± 0.680
F_5	2.4 ± 0.13	19.3 ± 0.012	99.5 ± 0.711
F_6	2.3 ± 0.15	19.4 ± 0.011	99.4 ± 0.651
F_7	2.2 ± 0.31	19.5 ± 0.021	101.4 ± 0.621
F_8	2.3 ± 0.42	19.3 ± 0.010	98.8 ± 0.521
F_9	2.4 ± 0.41	19.0 ± 0.012	100.9 ± 0.181
F_{10}	2.6 ± 0.33	19.1 ± 0.020	99.0 ± 0.101

***Values mentioned are average of 3 determinations**

- Disintegration test was evaluated for capsule as per USP in water, which shows disintegrate in the range of 4 mins 30 secs to 6 mins. Time taken for capsule shell broken, content in capsule dissolves, capsule shell washout were evaluated. The data was compiled in table -10.

Table:10 Disintegration time for Formulated capsules

Formulation Code	Disintegration Time for capsule (in minutes)		
	Capsule shell broken	**Content dissolves**	**Capsule shell washout**
F_1	1’02’’ ± 0.062	4’42’’ ± 0.011	6’02’’ ± 0.101
F_2	1’13’’ ± 0.17	4’36’’ ± 0.010	5’52’’ ± 0.180
F_3	0’53’’ ± 0.39	4’54’’ ± 0.012	6’04’’ ± 0.181
F_4	0’58’’ ± 0.07	5’02’’ ± 0.011	5’32’’ ± 0.180
F_5	0’55’’ ± 0.13	3’58’’ ± 0.012	4’48’’ ± 0.171
F_6	1’01’’ ± 0.15	4’46’’ ± 0.011	5’12’’ ± 0.151
F_7	1’12’’ ± 0.31	4’12’’ ± 0.021	5’26’’ ± 0.021
F_8	1’04’’ ± 0.42	4’03’’ ± 0.010	4’58’’ ± 0.121
F_9	0’58’’ ± 0.41	3’52’’ ± 0.012	4’37’’ ± 0.181
F_{10}	1’00’’ ± 0.33	4’02’’ ± 0.020	4’39’’ ± 0.101

***Values mentioned are average of 3 determinations**

7.5. IN VITRO RELEASE OF FENOFIBRATE CAPSULES:

In formulation F_1,F_2,F_3 formulations Poly Vinyl Pyrrolidine (K-25) was used in concentration of 4%, 6%, 8% and surfactant 4.5gm added in dry mix, the release was found to be 83.72%, 86.41% and 84.95% respectively. Hence, to improve release rate it was decided to alter the formulation further.

In F_4 formulation PVP K-25 - 6% and surfactant 4.5gm in binder solution was added and release was found to be 89.41%. In F_5, F_6, F_7 formulations only surfactant in different concentrations in dry mix: binder solution as 1:2, 2:1, 1.5:1.5 were used and release was found to be 96.34%, 95.44%, 93.36%.

To further improvement of dissolution profile, determined the granulation fluid content requirement for the effective release. In F_8, F_9, F_{10} formulations, addition of purified water for per capsule as 100mg, 80mg, 70mg were used and release was found to be 96.56%, 97.22%, 95.40%. The percentage of drug release increased with addition of surfactant in 1:2 concentrations and also for further improvement, optimized quantity of granulation fluid to be added. Higher dissolution profile also due to key role of addition of super disintegrant like crosscarmellose sodium has strong swelling property and highly porous structure of PVP K-25.

Table: 11 Dissolution data of F_1 Formulation:

S.No.	Time (mins)	Amount of drug release(mg)	Percentage drug release	Cumulative % drug release
1	10	54.42	27.21	27.21
2	20	82.84	41.42	41.45
3	30	136.74	68.37	68.41
4	40	154.96	77.48	77.55
5	50	161.24	80.62	80.70
6	60	167.28	83.64	83.72

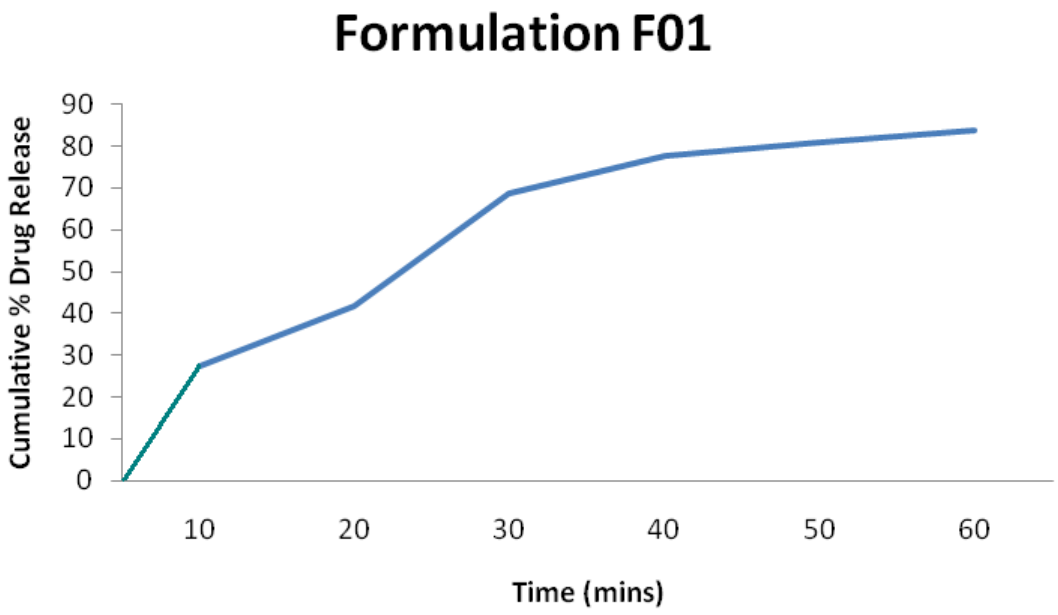


Fig: 12 Dissolution profile of F_1 Formulation

Table: 12 Dissolution data of F_2 Formulation:

S.No.	Time(mins)	Amount of drug release(mg)	Percentage drug release	Cumulative % drug release
1	10	66.72	33.36	33.36
2	20	102.94	51.47	51.50
3	30	133.04	66.52	66.57
4	40	149.28	74.64	74.71
5	50	167.82	83.91	83.99
6	60	172.64	86.32	86.41

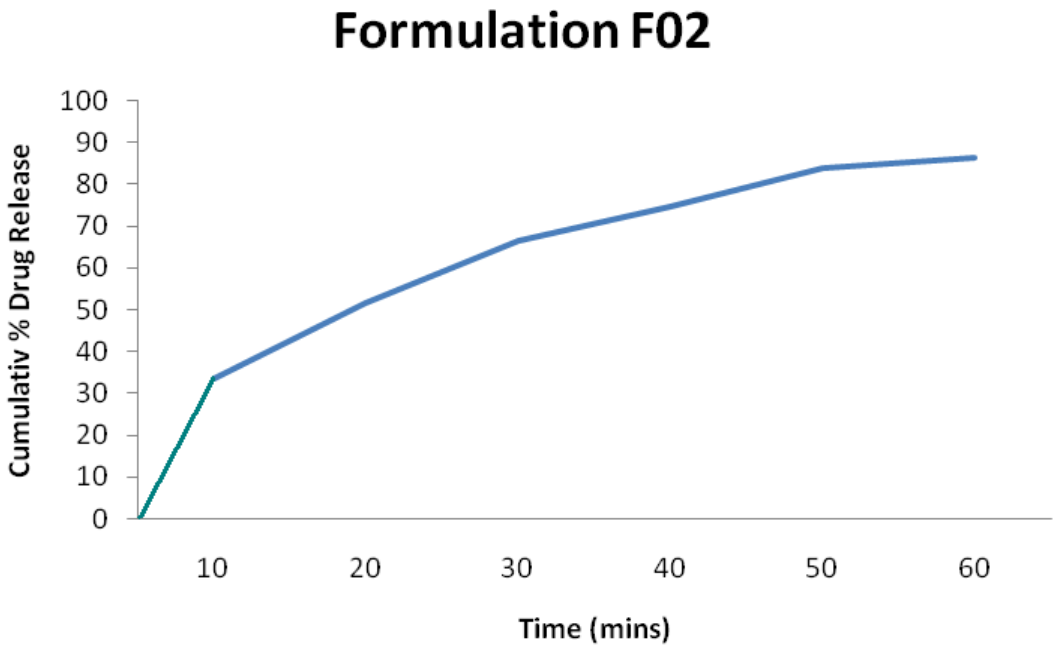


Fig: 13 Dissolution profile of F_2 Formulation

Table: 13 Dissolution data of F_3 Formulation:

S.No.	Time (mins)	Amount of drug release(mg)	Percentage drug release	Cumulative % drug release
1	10	53.44	26.72	26.72
2	20	95.68	47.84	47.86
3	30	141.26	70.63	70.68
4	40	152.54	76.27	76.34
5	50	164.72	82.36	82.44
6	60	169.72	84.86	84.95

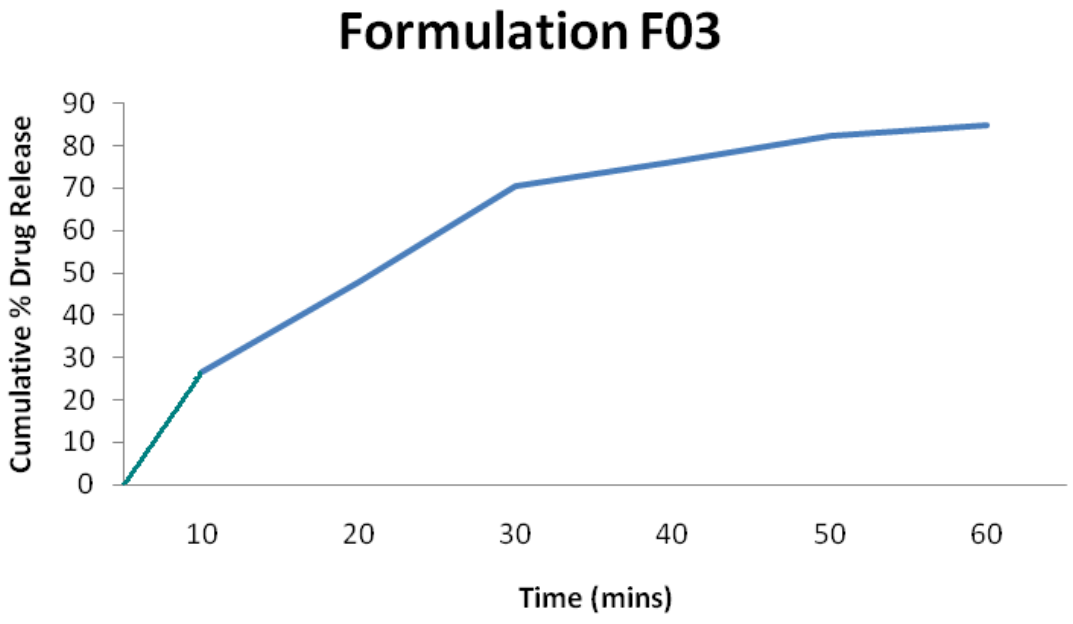


Fig: 14 Dissolution profile of F_3 Formulation

Table: 14 Dissolution data of F_4 Formulation:

S.No.	Time(mins)	Amount of drug release(mg)	Percentage drug release	Cumulative % drug release
1	10	77.26	38.63	38.63
2	20	99.02	49.51	49.55
3	30	144.92	72.46	72.51
4	40	163.44	81.72	81.80
5	50	175.82	87.91	88.01
6	60	178.64	89.32	89.41

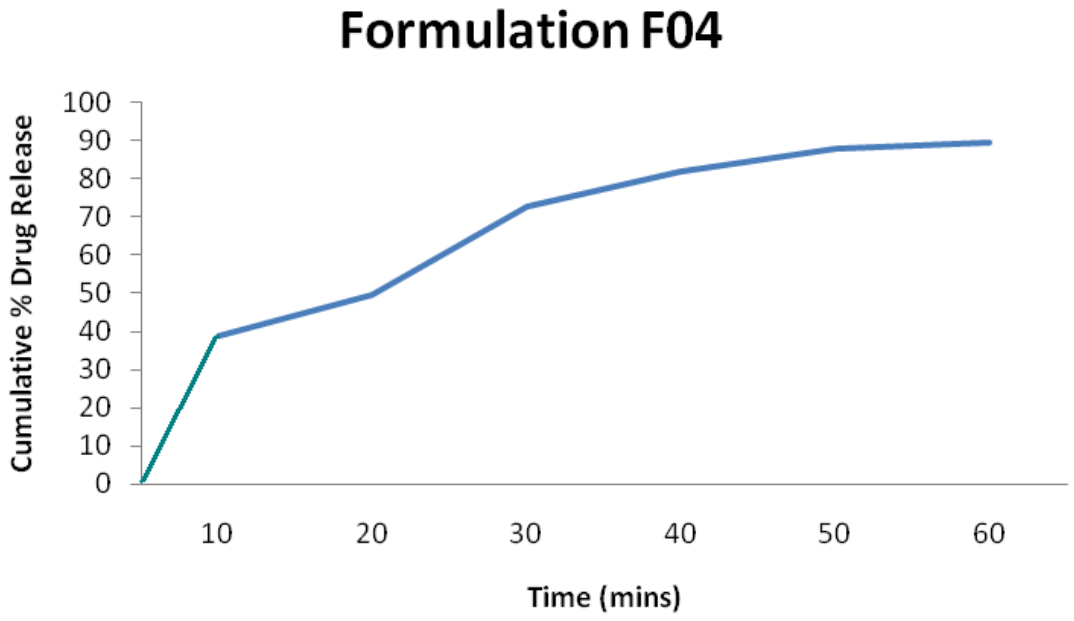


Fig: 15 Dissolution profile of F_4 Formulation

Table: 15 Dissolution data of F_5 Formulation:

S.No.	Time(mins)	Amount of drug release(mg)	Percentage drug release	Cumulative % drug release
1	10	83.42	41.71	41.71
2	20	129.84	64.92	64.96
3	30	156.24	78.12	78.19
4	40	172.54	86.27	86.35
5	50	186.64	93.32	93.41
6	60	192.48	96.24	96.34

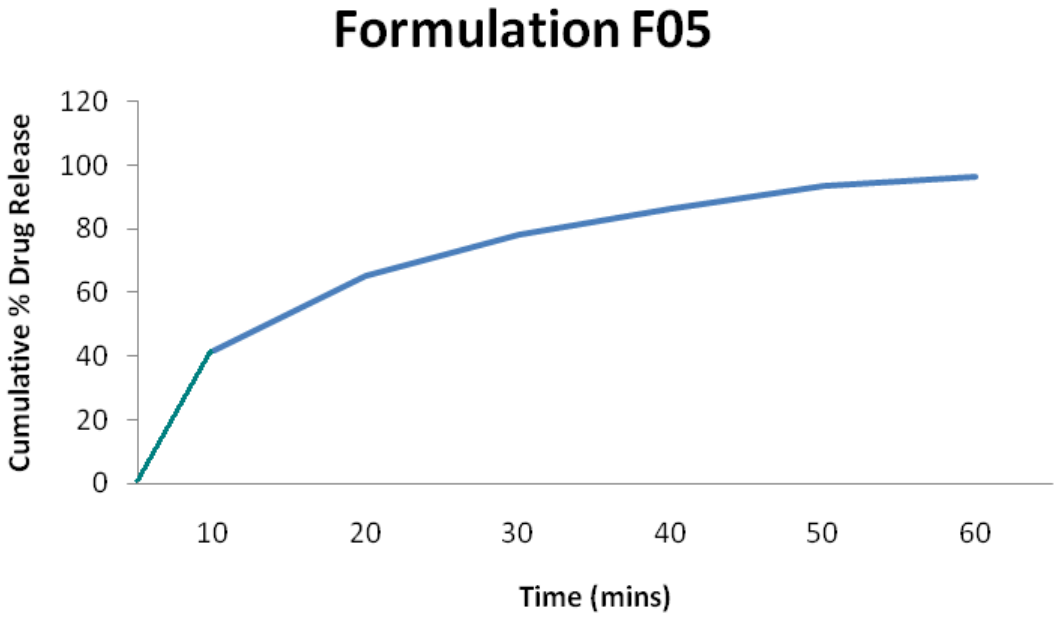


Fig: 16 Dissolution profile of F_5 Formulation

Table: 16 Dissolution data of F_6 Formulation:

S.No.	Time(mins)	Amount of drug release(mg)	Percentage drug release	Cumulative % drug release
1	10	78.16	39.08	39.08
2	20	124.24	62.21	62.25
3	30	158.74	79.37	79.43
4	40	179.08	89.54	89.62
5	50	185.28	92.64	92.73
6	60	190.68	95.34	95.44

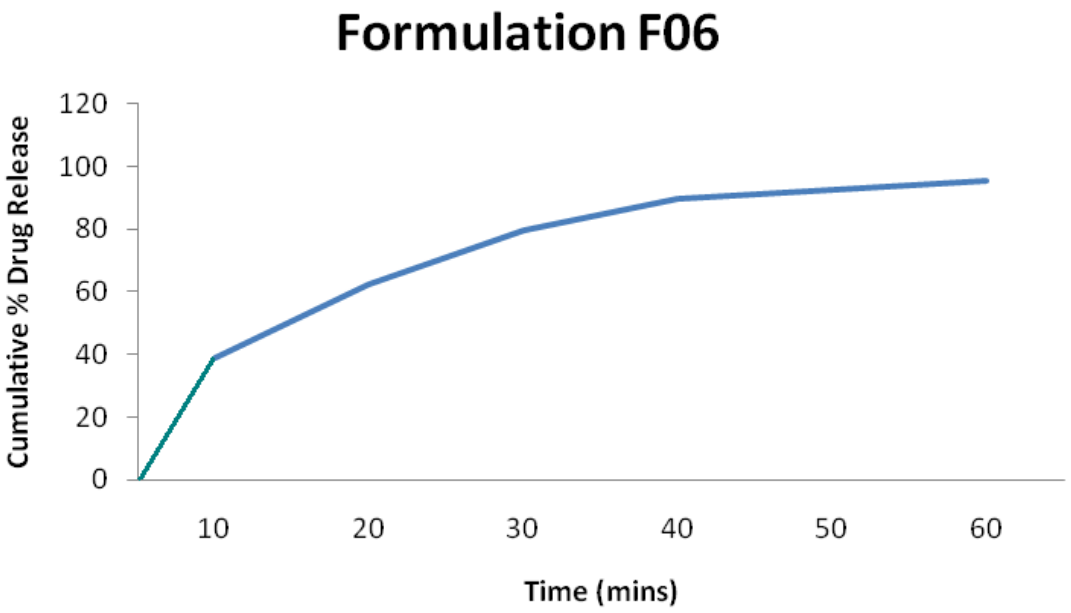


Fig: 17 Dissolution profile of F_6 Formulation

Table: 17 Dissolution data of F_7 Formulation:

S.No.	Time (mins)	Amount of drug release(mg)	Percentage drug release	Cumulative % drug release
1	10	74.38	37.19	37.19
2	20	112.54	56.27	56.31
3	30	128.74	64.37	64.43
4	40	177.24	88.62	88.69
5	50	180.64	90.32	90.41
6	60	186.52	93.26	93.36

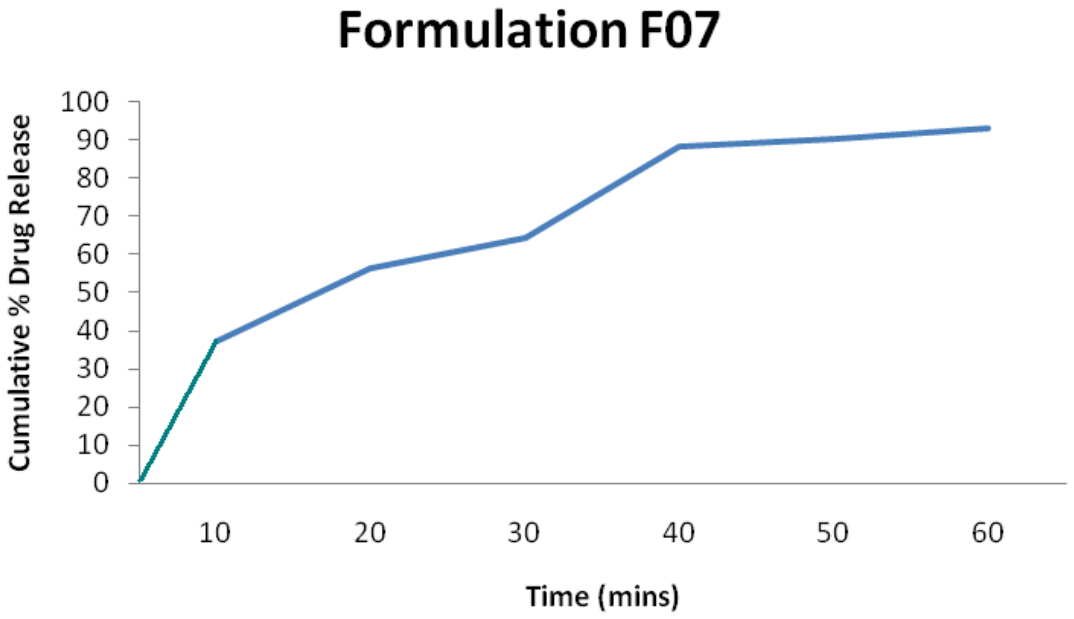


Fig: 18 Dissolution profile of F_7 Formulation

Table: 1 8 Dissolution data of F_8 Formulation:

S.No.	Time (mins)	Amount of drug release(mg)	Percentage drug release	Cumulative % drug release
1	10	80.80	40.40	40.40
2	20	134.38	67.19	67.23
3	30	160.42	80.21	80.28
4	40	182.14	91.07	91.15
5	50	187.42	93.71	93.81
6	60	192.92	96.46	96.56

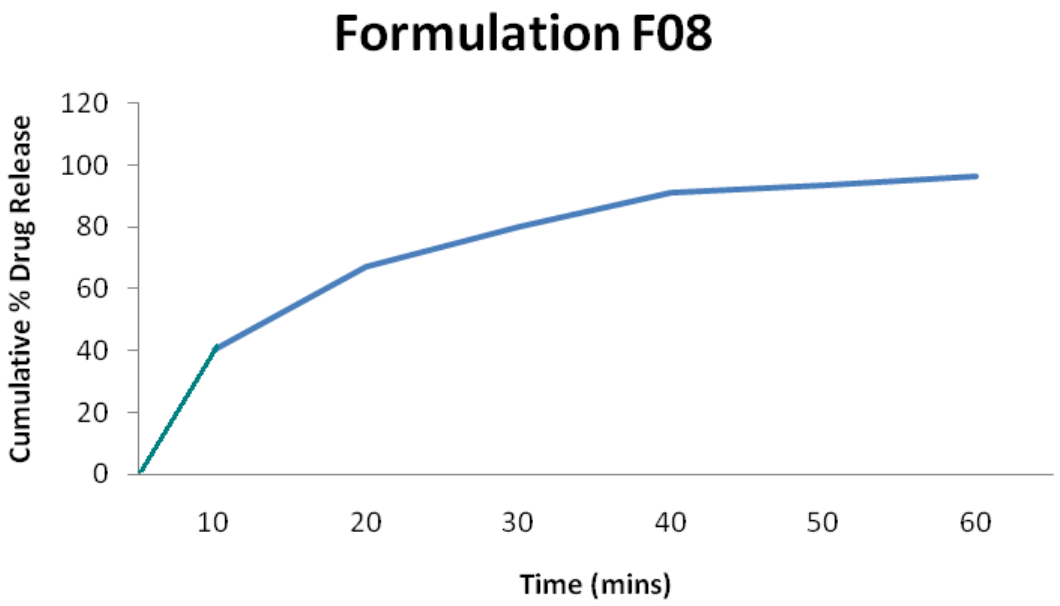


Fig: 19 Dissolution profile of F_8 Formulation

Table: 19 Dissolution data of F_9 Formulation:

S.No.	Time (mins)	Amount of drug release(mg)	Percentage drug release	Cumulative % drug release
1	10	83.80	41.90	41.90
2	20	116.84	58.42	58.46
3	30	145.68	72.84	72.90
4	40	170.82	85.41	85.49
5	50	187.24	93.65	93.74
6	60	194.24	97.12	97.22

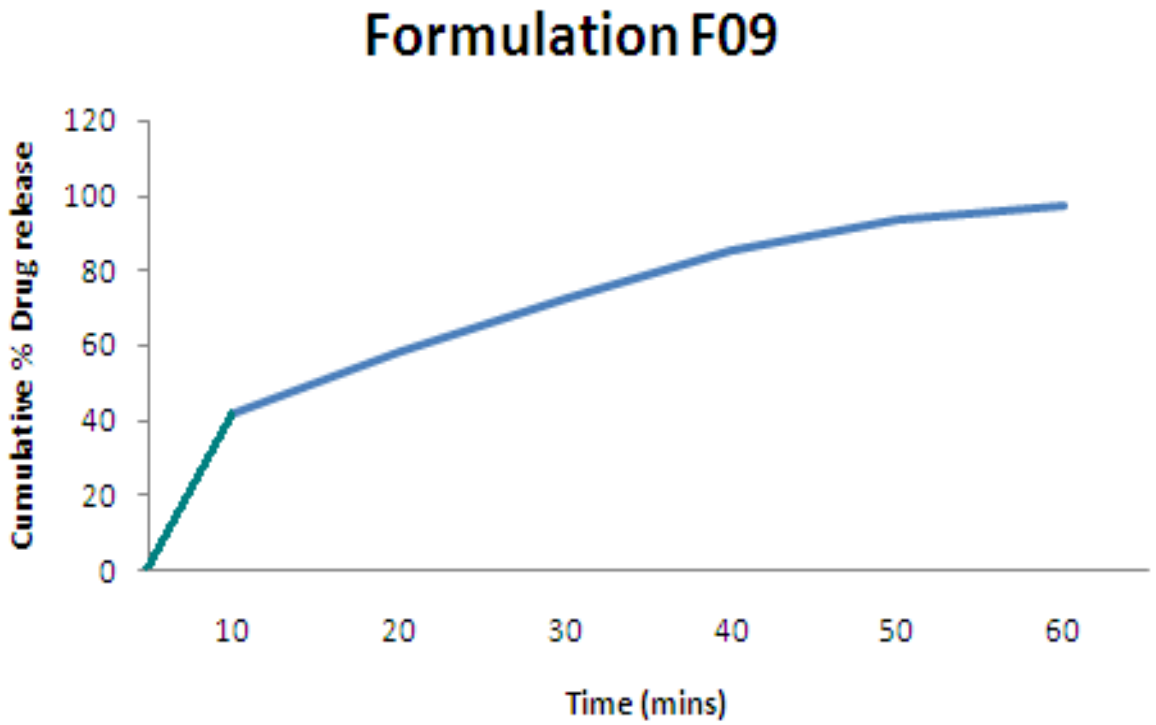


Fig: 20 Dissolution profile of F_9 Formulation

Table: 20 Dissolution data of F_{10} Formulation:

S.No.	Time (mins)	Amount of drug release(mg)	Percentage drug release	Cumulative % drug release
1	10	78.74	39.37	39.37
2	20	117.82	58.91	58.95
3	30	164.54	82.27	82.33
4	40	180.16	90.08	90.17
5	50	185.42	92.71	92.81
6	60	190.60	95.30	95.40

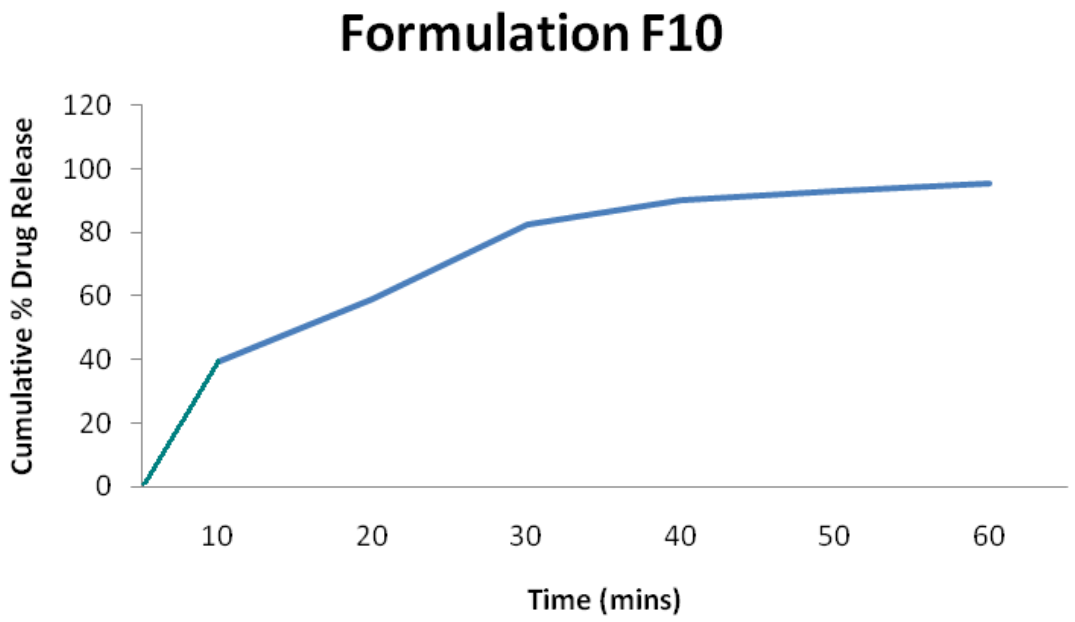


Fig: 21 Dissolution profile of F_{10} Formulation

Table: 21 Invitro Release Data of Innovator Sample:

S.No.	Time (mins)	Amount of drug release(mg)	Percentage drug release	Cumulative % drug release
1	10	76.90	38.45	38.45
2	20	114.42	57.21	57.25
3	30	144.88	72.44	72.50
4	40	170.24	85.12	85.20
5	50	185.70	92.85	92.94
6	60	193.44	96.72	96.82

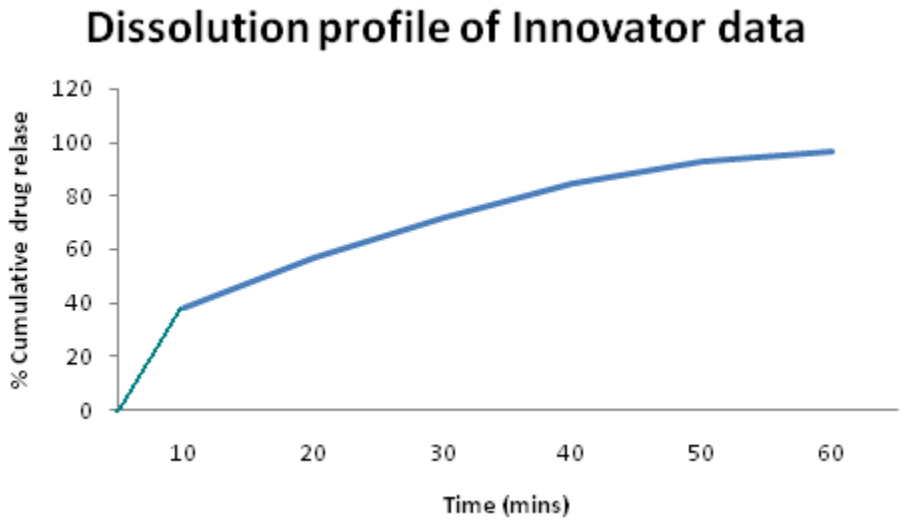


Fig: 22 Dissolution profile of Innovator data

10.6. SIMILARITY FACTOR (F_2):

When the similarity factor was found out by comparison of formulated product drug release rate with Innovator sample drug release rate. Similarity factor data for all the formulation compiled in table-22. Optimized formulation passes F_2 factor.

Table: 22 Similarity factor for formulated products

Formulation code	F01	F02	F03	F04	F05	F06	F07	F08	F09	F10
Similarity factor	23.14	34.36	34.56	43.63	54.89	49.78	44.14	68.61	71.12	64.14

7.7. ANALYSIS OF RELEASE DATA:

Table 23, 24, 25, 26 and Figure 23, 24, 25, 26 below shows the correlation coefficient of different kinetic models for fenofibrate optimized (F_9) formulation. Higuchi plots were found to be of linearity indicated that the drug release mechanism from these capsules by diffusion method. Moreover, *invitro* release of fenofibrate was best explained by Korsmeyer-Peppas equation also indicated a good linearity. The release exponent n was 0.491, which indicates a coupling of the diffusion and erosion mechanism so called anomalous diffusion or Non-Fickian transport. According to Korsmeyer-Peppas equation and indicated that value of “n” in Peppas equation is n = 0.45 to 0.89 indicates anomalous diffusion, which implies that the drug follows Non-Fickian transport.

A) Zero-Order Kinetics Plot:

Table:23 Zero-Order Kinetics Plot data for optimized (F_9) Formulation:

Time (mins)	Cumulative % drug release
10	41.90
20	58.42
30	72.84
40	85.41
50	93.65
60	97.12

Fig:23 Zero-order release profile of optimized (F_9) Formulation

Zero order release kinetics	
R^2	0.957

B) First-Order Kinetics Plot:

Table:24 First-Order Kinetics Plot data for optimized (F_9) Formulation:

Time (mins)	Log Cumulative % drug release
10	1.62
20	1.76
30	1.86
40	1.93
50	1.97
60	1.98

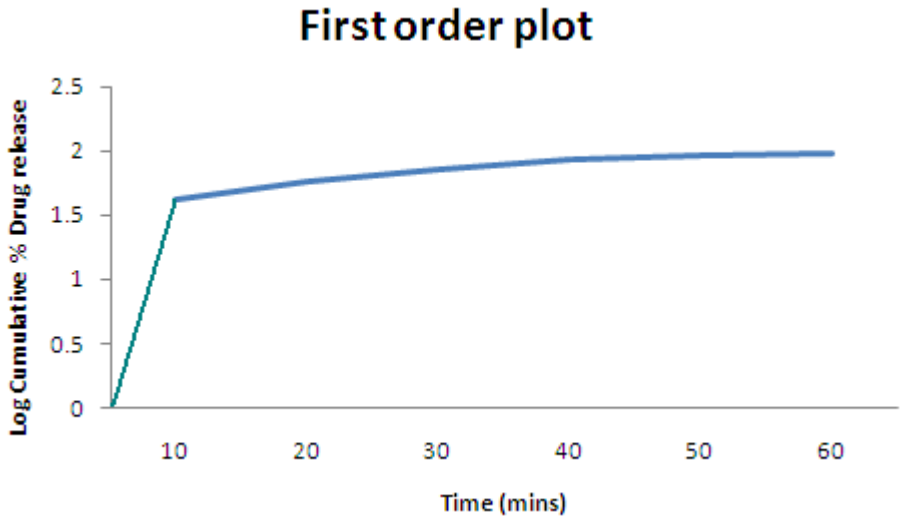


Fig:24 First-order release profile of optimized (F_9) Formulation

First order release kinetics	
R^2	0.904

C) Higuchi Plot:

Table:25 Higuchi Kinetics Plot data for optimized (F_9) Formulation:

SQRT of Time (mins)	Cumulative % drug release
3.16	41.90
4.47	58.42
5.48	72.84
6.32	85.41
7.07	93.65
7.75	97.12

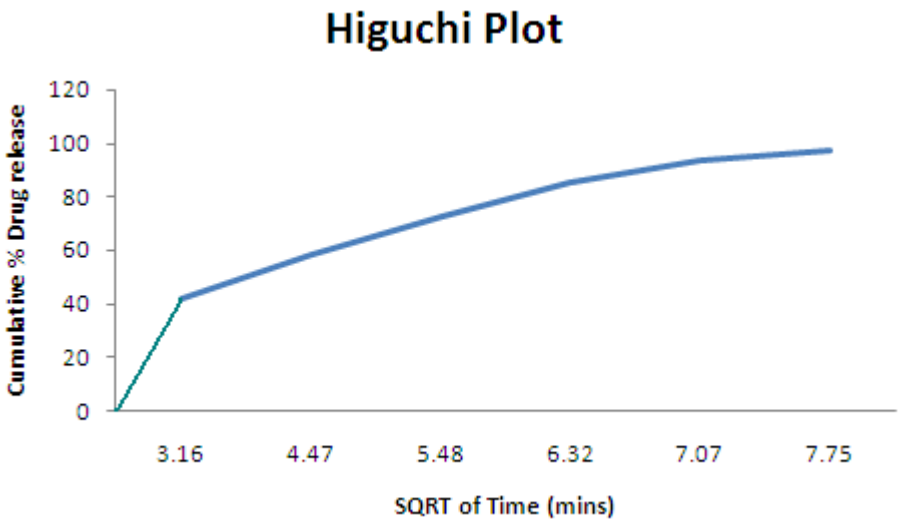


Fig:25 Higuchi release profile of optimized (F_9) Formulation

Higuchi release kinetics	
R^2	0.9893

D)Korsemeyer – Peppas model Kinetics Plot:

Table:26 Korsemeyer – Peppas model Kinetics Plot data for optimized (F_9) Formulation:

LogTime (mins)	Log Cumulative % drug release
1.00	1.62
1.30	1.76
1.47	1.86
1.60	1.93
1.69	1.97
1.77	1.98

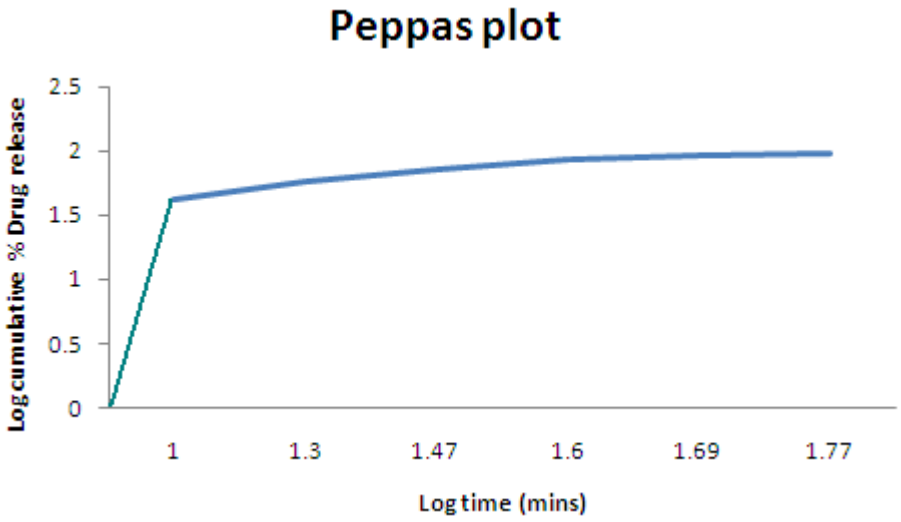


Fig:26 Korsemeyer – Peppas release profile of optimized (F_9) Formulation

Korsemeyer – Peppas model release kinetics	
R^2	n
0.9918	0.4917

7.8. DSC Curve:

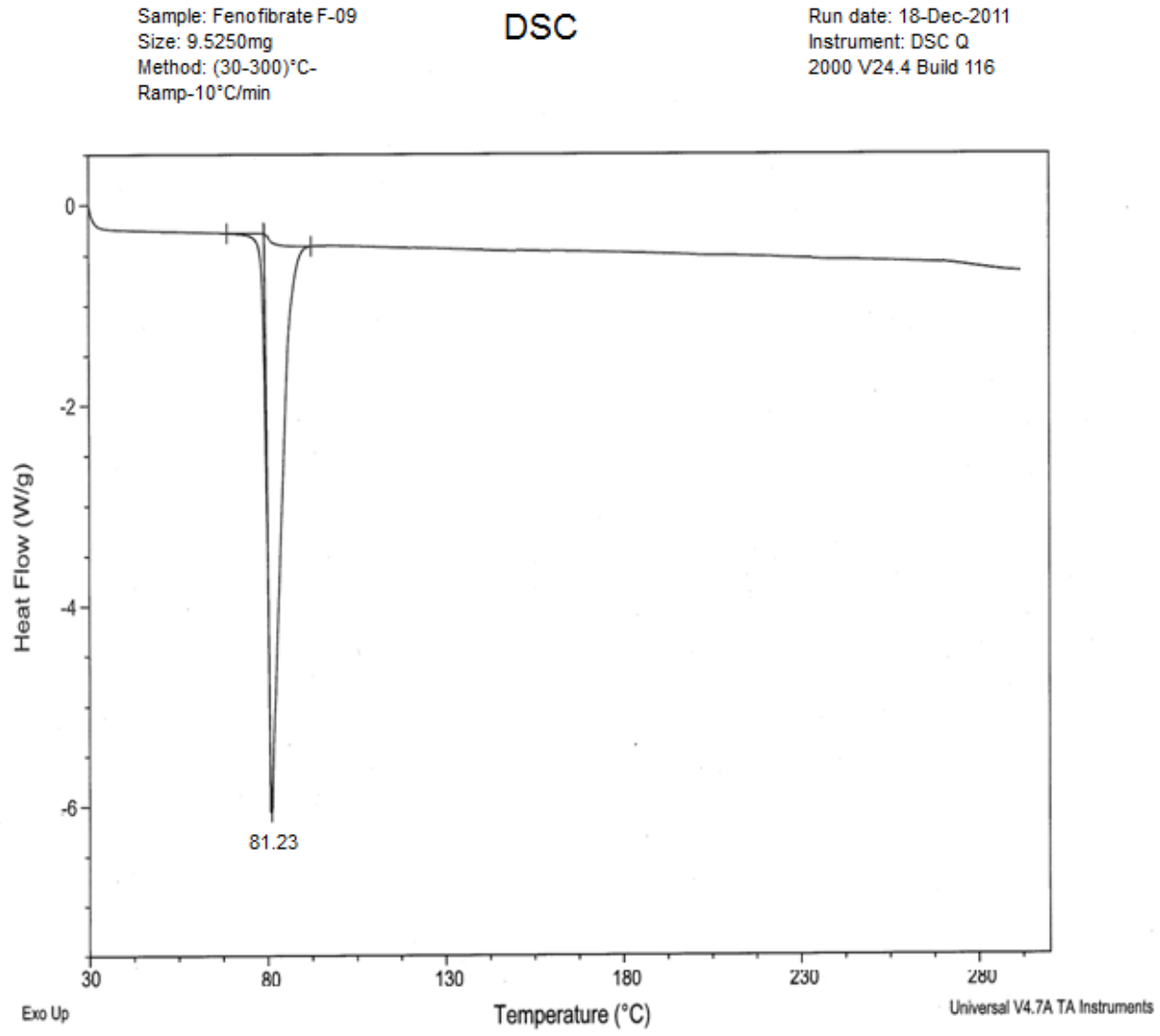


Fig:27 DSC curve of Fenofibrate API and Optimized formulation

Fenofibrate peak was clearly seen in its DSC thermogram indicating a sharp characteristic peak at temperature range 79-83^{0}C corresponding to its melting temperature (*Tm)*. This shows that Fenofibrate used was in pure form and indicates the crystalline nature of the drug. Also the DSC thermograms for F-09 showed characteristic peak in the same temperature range. The DSC analysis of physical mixture of drug and excipients revealed negligible change in the melting point of fenofibrate in the presence excipients, indicating no modification or interaction between the drug and excipients.

7.9. STABILITY STUDY:

Table:27 Stability study data at 25°C/60%RH for optimized formulation F_{09}

S.No.	Parameters		F_{09}	25°C/60%RH		
				At the end of 1st month	At the end of 2nd month	At the end of 3rd month
1.	Weight Variation (mg)		2.4	2.6	2.5	2.5
2.	Cap lock length (mm)		19.0	19.1	19.2	19.3
3.	Content Uniformity (%)		98.9	99.2	98.9	99.1
4.	Disintegration (mins)		4’37’’	4’34’’	4’36’’	4’35’’
5.	Dissolution Profile Data	Time(mins)	Cumulative percentage drug release			
		10	41.90	39.60	41.34	40.95
		20	58.42	56.32	57.42	57.32
		30	72.84	73.34	74.14	73.62
		40	85.41	87.31	86.47	86.12
		50	93.65	94.55	93.82	93.75
		60	97.12	97.62	96.99	97.04

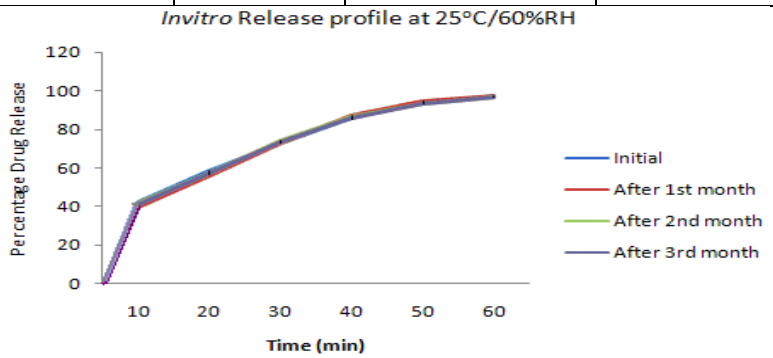


Fig.28 Comparison of *invitro* release profile at 25°C/60%RH for 3months

Table:28 Stability study data at 30°C/65%RH for optimized formulation F_{09}

S.No.	Parameters		F_{09}	30°C/65%RH		
				At the end of 1st month	At the end of 2nd month	At the end of 3rd month
1.	Weight Variation (mg)		2.4	2.5	2.4	2.5
2.	Cap lock length (mm)		19.0	19.3	19.0	19.2
3.	Content Uniformity (%)		98.9	99.1	98.7	99.0
4.	Disintegration (mins)		4’37’’	4’38’’	4’33’’	4’35’’
5.	Dissolution Profile Data	Time(mins)	Cumulative percentage drug release			
		10	41.90	40.60	41.54	40.88
		20	58.42	57.12	58.02	57.94
		30	72.84	72.34	73.54	73.12
		40	85.41	86.61	85.47	85.74
		50	93.65	93.55	94.28	93.12
		60	97.12	97.32	97.09	97.12

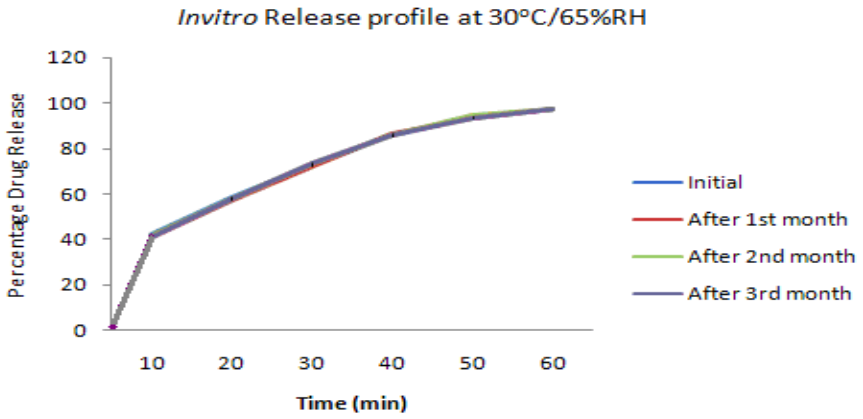


Fig.29 Comparison of *invitro* release profile at 30°C/65%RH for 3months

Table:29 Stability study data at 40°C/75%RH for optimized formulation F_{09}

S.No.	Parameters		F_{09}	40°C/75%RH		
				At the end of 1st month	At the end of 2nd month	At the end of 3rd month
1.	Weight Variation (mg)		2.4	2.5	2.8	2.6
2.	Cap lock length (mm)		19.0	19.1	19.0	19.2
3.	Content Uniformity (%)		98.9	99.0	98.7	99.2
4.	Disintegration (mins)		4’37’’	4’54’’	4’46’’	4’40’’
5.	Dissolution Profile Data	Time(mins)	Cumulative percentage drug release			
		10	41.90	41.32	41.64	41.21
		20	58.42	57.28	56.21	57.12
		30	72.84	72.74	74.14	73.33
		40	85.41	86.11	87.74	86.56
		50	93.65	94.15	94.12	94.02
		60	97.12	97.22	97.18	97.23

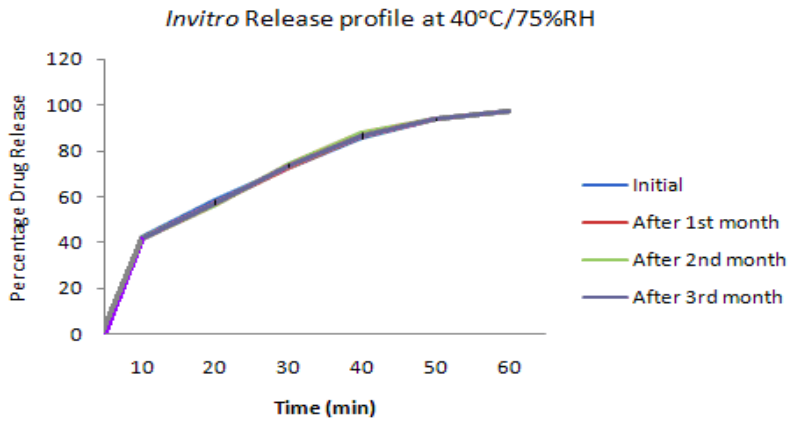


Fig.30 Comparison of *invitro* release profile at 40°C/75%RH for 3months

The optimized F_{09} formulation was subjected to accelerated stability conditions for 3 months at 25^{o}C/60% RH, 30^{o}C/65% RH, 40^{o}C/75% RH in a stability chamber (Osworld, Mumbai), At the interval of 1 month tablets were withdrawn and evaluated for various parameters like weight variation, Cap lock length, content uniformity, disintegration and dissolution. The tablets did not show any variation in the tested parameters and the results were within the limits.

10. CONCLUSION

BCS Class-II drug, Fenofibrate solubility as well as dissolution profile was improved by micronization, addition of surfactant and wet granulation method were prepared and formulated as capsule dosage form. Among these, F_{09} is considered to be the optimized formulation with the desired drug release and improved dissolution profile. The polymers which have been used in the best formulation (F09) are Polyplasdone, Microcrystalline cellulose, Starch and Poly vinyl pyrollidine with small quantity of granulating fluid.

The micronized fenofibrate analysed by FTIR, Compactibility study, Density parameter analysis, Solubility studies, Crystal properties, Particle size, Surface area and Analytical properties were evaluated, which shows better results than Non-micronized form.

The granules were evaluated for Physical parameters, Particle size distribution, Moisture content, Contact angle measurement and Related substances determination.

Dosage form evaluation parameters like Weight variation, Cap lock length indicated that the capsules so prepared were physically stable and complied with necessary Pharmacopoeial specification. Drug content uniformity also found to be under Pharmacopoeial specification.

The dissolution of all formulation was carried out as per Pharmacopoeial specification and data indicated that dissolution increased in all cases. Also shows that the drug release profile of the final optimized formulation was similar to that of marketed innovator product. It can be concluded that similar *in-vitro* release results will give similar *in-vivo* release profile.

DSC analysis reveals that there is no physical interaction between drug and excipients so there may not be chances of any incompatibility in the formulation. The phenomenon of optimized drug release follows Korsemeyer-Peppas model with non-fickian diffusion.

Stability testing of optimized formulation F_{09} at $25^{o}C$/60 % RH, $30^{o}C$ / 65% RH, $40^{o}C$/75% RH for 3 months did not show any variation in the tested parameters and release also.

11. BIBLIOGRAPHY

1. Brahmankar D M, Jaiswal S B., Textbook of Biopharmaceutics and Pharmacokinetics A Treatise, Vallabh Prakashan, New delhi, 2009, Ist edition, 19-22.

2. Leon Shargel, Susanna wu pong, Andrew B C Yu., Applied Biopharmaceutics and Pharmacokinetics, Mc Graw Hill, New delhi, 2005, 5th edition, 482-484.

3. Amidon G L, Lennernas H, Shah V P., Crison J R., Atheoretical basis for biopharmaceutic drug classification: the correlation of invitro drug product dissolution and invivo bioavailability, Pharm. Res., 1995, 12, 413-420.

4. http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm128219.html.

5. Abdou H M., Dissolution, Bioavailability and Bioequivalence, Mack Publication, Pennsylvania, 1989, Ist edition, 368.

6. Brahmankar D M, Jaiswal S B., Textbook of Biopharmaceutics and Pharmacokinetics A Treatise, Vallabh Prakashan, New delhi, 2009, 2nd edition, 25-29.

7. Cynthia K Brown, Hitesh P Chokshi., Acceptable analytical practices for – Dissolution testing of poorly soluble compounds, Pharm.Tech., Dec-2004, 4(2), 56-65.

8. Blagden N, De Matas M, Gavan P T, York P., Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates, Advanced Drug Delivery Reviews., May-2007, 12, 21-24.

9. Waard H D, Hinrichs L J, Visser M R., Unexpected differences in dissolution behavior of a tablet prepared from a solid dispersion with a surfactant physically mixed, Int. J. Pharm., 2006, 242, 150-162.

10. James swarbrick, J.E.Boylan., Encyclopedia of Pharmaceutical Technology, Vallabh Prakasan, New delhi, 2003, 14, 310-314.

11. Shabnam Ain, Qurratul Ain, Shama parveen., An overview on various approaches used for solubilization of poorly soluble drugs, T. Pharm. Res., 2009, 2, 84-104.

12. Tipnis H P, Amrita Bajaj., Principle and Application of Biopharmaceutics and Pharmacokinetics, Career Publication, Nashik, 2006, Ist edition, 275-279.

13. Fawaz F, Bonini F, Guoyt M., Bioavailability of norfloxacin from PEG 6000 solid dispersions and cyclodextrin inclusion complexes in the rabbits, Int. J. Pharm., 1996, 132, 271-275.

14. Aulton M E., Pharmaceutics, The science of dosage form design, Churchill Livingstone, London, 2007, 2nd edition, 160-165.

15. Hamsaraj Karanth, Vikram Subraya Shenoy, Rayasa Ramachandra Murthy., Industrially Feasible Alternative Approaches in the Manufacture of Solid Dispersions: A Technical Report, AAPS PharmSciTech., 2006, 7 (4), 87.

16. Swarbrick J, Boylan J C., "Granulation", Encyclopedia of pharmaceutical technology, Marcel Dekker INC, New York, 1992, 7, 121-123.

17. Libberman H A, Leon Lachmann, Joseph B S., Pharmaceutical dosage forms- Tablets, Marcel Dekker INC, New York, 1989, 2nd edition, 1,145-150.

18. Swarbrick J, Boylan J C., "Granulation", Encyclopedia of pharmaceutical technology, Marcel Dekker INC, New York, 1992, 7, 129-133.

19. Leon Lachmann, Libberman H A, Kanig J L., The theorey and Practice of Industrial pharmacy, Varghese publication, 1987, 3rd Edition, 318-325.

20. Summers M P.,"Granulation", Pharmaceutics, The science of Dosage Forms Design, Churchill livingstone, New York, 1988, 616-628.

21. Uhumwangho M U, Okor R S.: Modification of drug release from acetaminophen granules by melt granulation technique – Consideration of release kinetics, Pak. J. Pharm. Sci., 2006, 19(1), 22-27.

22. Remington: The science and practice of pharmacy by Lippincott Williams & Wilkins, 2005, 21st edition, 889-902.

23. Allen L V, Jr. Popovich N G and Ansel H C (Eds), Lippincott Williams & Wilkins, Ansel's Pharmaceutical Dosage Forms & Drug Delivery Systems, 8th edition, 2005, 205-211.

24. Jones B E, Seager H.,"Capsules", Pharmaceutics, The science of Dosage Forms Design, Churchill livingstone, New York, 1988, 325-327.

25. Swarbrick J, Boylan J C., "Capsules, Hard", Encyclopedia of pharmaceutical technology, Marcel Dekker INC, New York, 1992, 2, 251-254.

26. http://capsugel.com?media/library/the-hard-gelatin-capsule-advantage.pdf.

27. PamulaReddy Bhavanam, Subhaskar Reddy, Ravikanth V, Surender G., Formulation and evaluation of Fenofibrate tablets using different binding agents, Int. J. Innov. Pharm. Res., 2010, 1(1), 33-36.

28. Ravi Kumar, Swati Patil , Patil M B, Sachin R Patil, Mahesh S P., Formulation Evaluation of Mouth Dissolving Tablets of Fenofibrate Using Sublimation Technique, Int.J. ChemTech Res., 2009, 1(4), 840-851.

29. Ashok R Patel and Pradeep R Vavia., Preparation and invitro evaluation of self-micro emulsifying drug delivery system using fenofibrate, AAPA J., Sep-2007, 9(3), 344-352.

30. Pasut R, Hector G, Arthur B, Tokarcyzk., A high-throughput approachapproach towards a novel formulation of fenofibrate in omega-3 oil, Eur. J. Ph. Sci., Apr-2008, 33, 4-5 and 351-360.

31. Rajeev A. Jain, Luis Brito, Julie Straub, Todd Tessier, Howard Bernstein A., Effect of powder processing on performance of fenofibrate formulations, Eur. J. Phar. & Biophar., June2008, 69(2), 727-734.

32. Liandong Hu, Hongyu wu, Feng niu., Design of fenofibrate microemulsion for improved bioavailability, Int. j. phar., Sep-2010, 396, 1-2, 345-349.

33. Ganesh P S, Ram B G., Dissolution rate enhancement of fenofibrate by adsorption onto silica using supercritical carbondioxide, Int. j. phar., Aug-2008, 360, 1-2, 213-218.

34. Zengrong Jia, Ping lin, Yu xiang, Xuan Zhang., A novel nanomatrix system consisted of colloidal silica and pH sensitive polymethacrylates improves the oral bioavailability of fenofibrate, Eur. J. Phar. & Biophar., Sep-2011, 79(1), 126-134.

35. Yaping chen, Yi lu, Jie lai, Jing sun, Wei Wu., Enhanced bioavilability of the poorly water soluble drug fenofibrate by using liposomes containing a bile salts, Int. j. phar., July 2009, 376, 1-2, 153-160.

36. Markus Vogt, Klaus Kunath, Jennifer B D., Disoolution enhancement of fenofibrate by micronisation, co-grinding and spray-drying: Comparison with commercial preparations, Eur. J. Phar. & Biophar., Feb-2008, 68(2), 283-288.

37. Qiao-Ping Huang, Jie-xing Wang, Zin-bing zhang, Jimmy yun., Preparation of ultrafine fenofibrate powder by solidification process from emulsion, Int. j. phar., Feb-2009, 368, 1-2, 160-164.

38. Ming-Thau Sheu, Ching-Min, Theodore D S., Characterization and dissolution of fenofibrate solid dispersion systems, Int. j. phar., Mar-1994, 103(2), 137-146.

39. Srinarong P, Faber J H, Visser M R, Frijlink H W., Strongly enhanced dissolution rate of fenofibrate solid dispersion tablets by incorporation of superdisintegrants, Eur. J. Phar. & Biophar., Sep-2009, 73(1), 154-161.

40. Vinayak P S, Damon smith, Jean-christophe Leroux., Enhancement of oral bioavilability of poorly water soluble drugs by Poly(ethylene glycol)-*block*-poly(alkyl acrylate-*co*-methacrylic acid) self-assembles, Jr. cont. Rel., May-2005, 104(2), 289-300.

41. Michiel Van, Randy M, Raf mols, Thao do thi., Enhanced absorption of the poorly soluble drug fenofibrate by tuning its release rate from ordered mesoporous silica, Eur. J. Phar. Sci., Dec-2010, 41(5), 623-630.

42. Markus vogt, Maria Vertzoni, Klaus Kunath., Cogrinding enhances the oral bioavailability of EMD 57033, a poorly water soluble drug, in dogs, Eur. J. Phar. & Biophar., Feb-2008, 68(2), 338-345.

43. Xi Han, Chinmay Chorol, Daniel to, Yuhua Chen., Simultaneous micronisation and surface modification for improvement of flow and dissolution of drug particles, Int. j. phar., Aug-2011, 415(2), 185-195.

44. Mohammad B J, Hadi V, Mohammad-Reza, Khosro A, Ghobad M., Cogrinding as an approach to enhance dissolution rate of a poorly water-soluble drug, Powder Technology, Jan-2010, 197(3), 150-158.

45. Wong S W, Kellaway I W, Murdan S., Enhancement of the dissolution rate and oral absorption of a poorly water soluble drug by formation of surfactant- containing microparticles, Int. j. phar., July-2006, 317(1), 61-68.

46. Markus Vogt, Klaus Kunath, Jennifer B D., Dissolution enhancement of four poorly water soluble by cogrinding with commonly used excipients, Eur. J. Phar. & Biophar., Feb-2008, 68(2), 330-337;.

47. Stephen B R, Bozena K M, Yvetta A G., Design and characterization of a surfactant - enriched tablet formulation for oral delivery of a poorly water soluble immunosuppressive agent, Int. j. phar., May-1999, 182(2), 173-186.

48. Bolhuis G K, Zuurman K, Wierik H p., Improvement of dissolution of poorly soluble drugs by solid deposition on a super disintegrant II. The choice of super disintegrant and effect of granulation, Eur. J. Phar. & Biophar., Mar-1997, 5(2), 63-60.

49. Akio Miwa, Toshio Y, Shigeru I., Prediction of suitable amount of water addition for wet granulation, Int. j. phar., Feb-2000, 195, 1-2, 81-92.

50. Beatrice A, Cristina C, Nadia P., Evaluation of β-lactose, PVP K12 and PVP K90 as excipients to prepare piroxicam granules using two wet granulation techniques, Eur. J. Phar. & Biophar., Nov-2003, 56(3), 479-487.

51. Kreutzwald P, Malinovskaja K, Veski P., Effects of diluents and disintegrants on the release of poorly soluble drugs from hard gelatin capsules, Eur. J. Phar. Sci., Sep-2007, 32(1), 49-50.

52. Ojantakanen S, Marvola M, Hannula M, Klinge E., Bioavailability of ibuprofen from hard gelatin capsules containing different viscosity grades of HPMC and SCMC, Eur. J. Phar. Sci., June 1993, 1(2), 109-114.

53. Guyot M, Fawaz F, Maury M., Invitro release of theophylline from cross-linked gelatin capsules, Int. j. phar., Nov-1996, 144(2), 209-216.

54. Ambrus R, Aigner Z, Catenacci L., Physio-chemical characterization and dissolution properties of Nifluminic acid-cyclodextrin-PVP ternary system, Jour. of therm. anal. & calorimetry., 2007, 104(1), 291-297.

55. Alia A. Badawi, Mohamed Ahmed, Doaa Ahmed, Sami A A., Characterization and stability testing of itraconazole solid dispersions containing crystallization inhibitors, American Journal of Drug Discovery and Development., 2011, 1, 144-159.

56. Ahuja N, Katare O P, Singh B., Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers, Eur J Pharm Biopharm., 2007, 65, 26-38.

57. Sherif I F B, David B G and Munir A. H., A Study on the Effect of Wet Granulation on Microcrystalline Cellulose Particle Structure and Performance, Pharm. Research, 2006, 23(3), 634-640.

58. Guo M, Augsburger LL., Potential application of silicified microcrystalline cellulose in direct-fill formulations for automatic capsule-filling machines, Pharm Dev Technol., 2003, 8(1), 47-59.

59. Simon M. I, James D. L, Karen H, Bryan J., Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review, Powder Technology, June 2001, 117(1), 3-39.

60. Naveen P, Anuj K, Vishal M, Pankaj P and Rama T., Formulation and optimization of immediate release tablet of an antialcohlic drug by dry granulation method, IJCP 2011, 3 (08), 34-37.

61. Limin Shi, Yushi Feng, Changquan Calvin Sun., Origin of profound changes in powder properties during wetting and nucleation stages of high-shear wet granulation of microcrystalline cellulose, Powder Technology, 2011, 208, 663–668.

62. Biljana G, Rade I, Rok D and Stane S., Formulation and evaluation of immediate release tablets with different types of paracetamol powders prepared by direct compression., Afr. J. Pharm. Pharmacol., Jan- 2011, 5(1), 31-41.

63. Suhas M. K, Vinodh S, Mannur, Ketan B R., Formulation and evaluation of mouth dissolving tablets of losartan potassium by direct compression techniques, Int. J. Res. Pharm. Sci., 1(3), 290-295, 2010 .

64. Venkata Ramana Reddy., Development and characterization of taste masked compressed odt formulation of low bitter drug. Publication Ref No.: IJPRD/2010/PUB/ARTI/VOV-2/ISSUE-9/NOV/019, ISSN 0974 – 9446.

65. Preetha B, Pandit K, Bindu K, Rajesh V and Balasubramaniam J., Comparative Evaluation of Mode of Incorporation of Superdisintegrants on Dissolution of Model drugs from wet granulated tablets, Acta Pharmaceutica Sciencia, 2009, 50, 229-236.

66. Garry Hollenbeck., Bioavailability of phenylpropanolamine HC1 from tablet dosage forms containing croscarmellose sodium, Int. j. phar.,1998, 47, 89-93.

67. Ferrero C, Mufioz N, Velasco M V, Mufioz-Ruiz A., Disintegrating efficiency of croscarmellose sodium in a direct compression formulation, Int. j. phar., 1997, 147, 11- 21.

68. Nagasamy D, Sankar S, Meyyanathan S N, Elango K, Suresh B and Santhi K., Design and Development of Prochlorperazine Maleate Sustained Release Tablets: Influence of Hydrophilic

Polymers on the Release rate and *In vitro* Evaluation, International Journal of Pharmaceutical Sciences and Nanotechnology, Sep-2010, 3(2), 45-52.

69. Graham B, Akintayo A, Mark S, Ameet A., HyperDSC studies of amorphous poly vinyl pyrrolidone in a model wet granulation system., Int. j. phar., 2006 312, 61–65.

70. Yadav VB , Yadav AV., Enhancement of solubility and dissolution rate of indomethacin with different polymers by compaction process, Int.J. ChemTech Res.2009,1(4), 1072-1078.

71. James D O, Robert P J, James J, David G, Michael J, Agba D., Binder addition methods and binder distribution in high shear and fluidised bed granulation, chemical engineering research and design, 2011, 89, 553–559.

72. Chowdary R, Veeraiah E and Siva kumar P., Formulation development of nimesulide tablets by wet granulation and direct compression methods employing starch phosphate., Int. J. Chem. Sci., 2011, 9(4), 1595-1606.

73. Vikas A S, Vipin K, Mahesh K, Manoj G, Pratim K C., Dissolution Enhancement of Drugs.Part I: Technologies and Effect of Carriers, International Journal of Health Research, June 2009, 2(2): 107-124.

74. Karen P H, Batool K., Granulation of hydrophobic powders, Powder Technology, 2009, 189, 253–262.

75. Musa El-Barghouthi and Ala'a Eftaiha., A Novel Superdisintegrating Agent Made from Physically Modified Chitosan with Silicon Dioxide, Drug Development and Industrial Pharmacy, 2008, 34,373–383.

76. Jen-Sen Wu, Hsiu-O Ho, Ming-Thau Sheu., Influence of wet granulation and lubrication on the powder and tableting properties of codried product of microcrystalline cellulose with b-cyclodextrin, Eur J Pharm Biopharm., 2001, 51, 63-69.

77. Vikas anand., Dissolution rate enhancement of BCS class II drugs by order mixing, Int J Comp. Pharm., ISSN 0976-8157, 01, 2011.

78. Karmarkar A B, Gonjari I D, et al., Use of melt solidification technique for preparation of fenofibrate beads: A technical note, Digest Journal of Nanomaterials and Biostructures., June 2009, 4(2), 291 – 297.

79. Ravi kumar, Swati patil, Patil M B, Patil S R., Formulation evaluation of mouth dissolving tablets fenofibrate using sublimation techniques, Int J Chemtech Res., 2009, 1(4), 840-850.

80. Wendy, Wilson, Yun Peng, et al., Generalization of a prototype intelligent hybrid system for hard gelatin capsule formulation development, AAPS PharmSci Tech., 2005, 6(3), E449-453.

81. Krishna Gupta, Askarkar, Rathod, Wadodkar., Validated spectrophotometric determination of fenofibrate in formulation, Der Pharmacia Sinica., 2010, 1(1), 173-178.

82. Wong S W, Kellaway I W, Murdan S., Enhancement of the dissolution rate and oral absorption of poorly soluble drugs by formation of surfactant containing microparticles, Int. J. Pharm, 2006, 317, 61-68.

83. Pauline M et al., Fenofibrate raw materials: HPLC methods for assay and purity and an NMR method for purity, J. Pharm. Biomed. Anal., 1998, 18, 383-402.

84. http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm?PrintAll=1.

85. Youdef J et al., Liquisolid technique as a new approach to sustain propanol HCL release from tablet matrices, Int j Pharm., 2008, 362, 102-108.

86. Basak S C, Senthil kumar K, Ramalingam M.: Design and release characteristics of sustained release tablets containing metformin HCl, Braz J Pharm Sci., 2008, 44(3), 477-450.

87. Patel Tejas, Patel L D, Patel Timir, et al., Dissolution enhancement of fenofibrate by solid dispersion technique, Int. J. Pharm. Sci., 2010, 1(2), 127-132.

88. www.ich.org/products/guidelines/quality.html.

1. INTRODUCTION

Modern drug design not only pays attention on biological activity of a drug but also take in to account its ability to get absorbed and available in systemic circulation. Since the oral route of drug administration is often favored by the patients; therefore the main goal in the process of drug development is to obtain a drug product with a good oral bioavailability.

Bioavailability is defined as the rate and extent amount of active pharmaceutical ingredients, which reaches the systemic circulation from formulated products and also reaches the site of action. Oral bioavailability of drug is affected by variety of factor, which influence their absorption from the G.I.T. One of the rate determinant factors for absorption is drug dissolution, which is influenced by the solubility of the drug in G.I. fluid.

The chains of events that occur following administration of solid dosage form until its absorption into systemic circulation are depicted in Figure no:1.

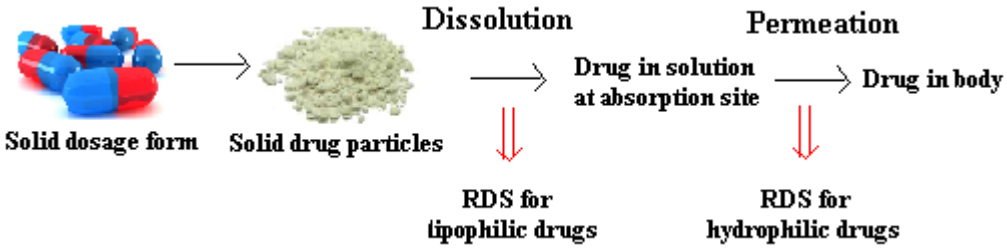


Fig.1 Rate determining steps for Bioavailability of drugs

The two critical rate-determining steps in the absorption of orally administered drugs are[1]:

1. Rate of dissolution and
2. Rate of permeation through biological membrane.

1.1 BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

To solve the bioavailability problem US-FDA classified the drugs under Biopharmaceutics classification system (BCS) based on the parameters of solubility, permeability and dissolution[2]. The Biopharmaceutics classification system is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. According to BCS, drug substances are classified as follows[3]:

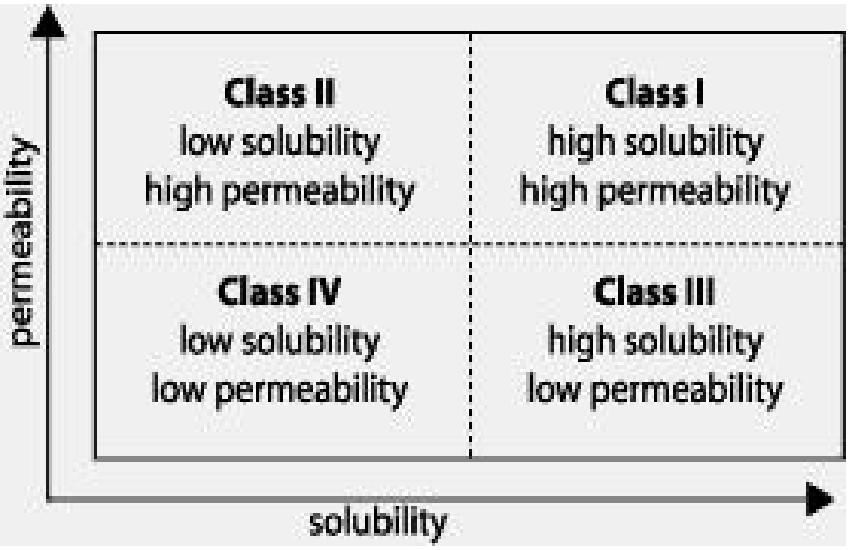


Fig.2 Classification of drugs based on BCS

CLASS BOUNDARIES[4]:

- A drug substance is considered HIGHLY SOLUBLE when the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5.
- A drug substance is considered HIGHLY PERMEABLE when the extent of absorption in human is determined to be > 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose.
- A drug product is considered to be RAPIDLY DISSOLVING when > 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of < 900 ml buffer solutions.

1.2 BCS CLASS-II DRUGS

One of the major current challenges of pharmaceutical industry is related to strategies that improve the water solubility of poorly soluble drugs. Most of the API's currently under development are BCS class–II compounds. More than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble categories. For poorly water soluble and highly lipophilic drug candidates, dissolution in G.I fluid is the rate-limiting step in absorption. Drug substance with an aqueous solubility of less than 1mg/ml may represent a potential bioavailability problem, so there is need to improve its solubility[5]. Poorly water soluble drugs often require higher doses in order to reach therapeutic plasma concentrations after oral administration.

This resulting predominance of BCS class-II compound in pharmaceutical development "pipeline" make it apparent that the concept of solubility, the process of dissolution must be understood to establish novel strategies for optimization of these factors. The various factor, prime importance is drug solubility. Almost every factor that affects dissolution rate, influences the drug solubility in one way or other. An empirical relation which is useful to predict the dissolution rate of a drug from its solubility is;

$$R = dc/dt = 2.24\ Cs$$

Where,

R = dc/dt = dissolution rate of the drug

Cs = Saturation or maximum drug solubility

It has been shown that a drug should have a minimum aqueous solubility of 1% to avoid bioavailability problems[6].

Absolute / intrinsic solubility is defined as the maximum amount of solute dissolved in a given solvent under standard conditions of temperature, pressure and pH. Solubility is usually determined by measuring the concentration of a saturated solution after equilibration at 37^0C for 1 hr to 24 hr. The equilibration time depends on the test duration time as well as physical and chemical stability of drug[7].

1.3 TECHNIQUES TO IMPROVE THE SOLUBILITY OF DRUGS

Nowadays, pharmaceutical technology provides many approaches to enhance the dissolution rate of poorly soluble drugs. To improve the solubility or to increase the availability surface area for dissolution is:

I – Physical modification:

A) Particle size reduction:

Particle size and effective surface area of solid drugs are inversely related to each other. Smaller the drug particle, greater the surface area. According to the modified Noyes-Whitney equations,

$$\text{Dissolution rate} = dc/dt = DAK_{W/O}(Cs\text{-}Cb)/\ Vh$$

D – diffusion coefficient of the drug;

A – Surface area of the dissolving solid;

$K_{W/O}$ – Intrinsic dissolution rate constant;

V – Volume of dissolution medium;

h – Thickness of stagnant layer;

(Cs-Cb) – Concentration gradient for diffusion of drug.

From above equation it is clear that larger the surface area, higher the dissolution rate. Since the surface area increases with decreasing particle size, which can be accomplished by micronisation or nanonisation, will result in higher dissolution rates.

Micronisation is the process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by spray drying or by use of attrition methods (fluid energy or Jet mill). The process is called micro-milling. The solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug[8]. Conventional methods of particle size reduction, such as comminution

and spray drying, rely upon mechanical stress to disaggregate the active compound. The micronisation is used to increased surface area for dissolution.

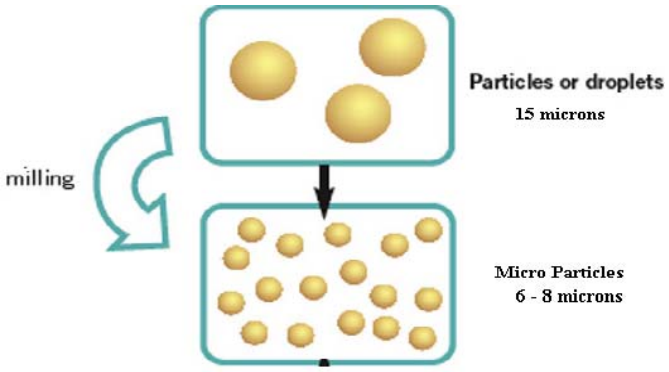


Fig.3 Micronisation of drug particles

Nanonisation is a process whereby the drug powder is converted to nanocrystal of size 200-600nm. The main production technologies currently is use to produce drug nanocrystal yield as a product a dispersion of drug nanocrystal in a liquid, typically water called nanosuspension. Techniques for the production of nanosuspension are homogenization and wet milling.

Other techniques for reduction of the particle size are **sonocrystallisation, supercritical fluid process, spray drying.**

B) Solubilisation[9]:

Surfactants are substances, which at low concentrations adsorb on to the surface or intersurface of a system. Surface-active agents have a characteristics structure possessing both polar and non-polar regions in the same molecule. Surfactants are classified as follows:

1. Anionic surfactant (COO^-, SO_3^-, OSO_3^-): Sodium lauryl sulphate,
2. Cationic surfactant (N^+Cl^-): Cetrimide
3. Ampholytic surfactant: N-deodecyl- N, N- dimethylbetaine
4. Nonionic surfactant: Poloxamer

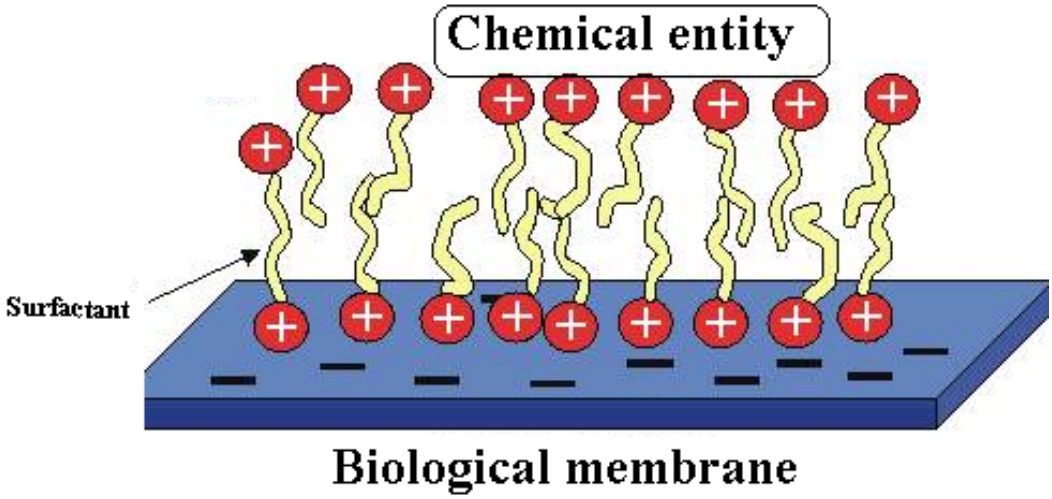


Fig.4 Effect of surfactant on Drug and biological membrane

Surfactant system may change ADME properties of co-administered drug, also penetrate and disrupt biological membrane. Anionic surfactant shows enhancements in intrinsic dissolution rate of 500 to 2000 fold than in buffer alone. Solubiliztion in surfactant aqueous systems above the CMC offers one pathway for the formulation of poorly soluble drugs[10].

Use of surfactants as absorption enhancer, which enhance both dissolution rate as well as permeability of drug. They enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid drug particles. When small apolar molecules are added they can accumulate in the hydrophobic core of the micelles[11]. It also improves stability through micellization.

Use of cosolvent system can increase the water solubility of a drug significantly. But the choices of biocompatible solvents are limited, such as to glycerine, propylene glycol, dimethylsulfoxide, ethanol and N, N dimethylformamide etc.

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs.

C) Modification of crystal habit:

Depending upon the internal structure of the solid drug, selection of proper form of drug with greater solubility is important. In general, amorphous are more soluble than metastable polymorphs, anhydrates are more soluble than hydrates and solvates are more soluble than non-solvates. Amorphous form of the drug demonstrate faster dissolution rate than crystalline forms[12].

D) Complexation

The most common complexing ligands are cyclodextrins, caffeine, urea, polyethylene glycol, N methylglucamide. cyclodextrin are unique since they increase the water solubility of poorly soluble drugs by fitting them into the hydrophobic cavity of the cyclodextrin molecule. Thus the molecularly encapsulated drug has greatly improved aqueous solubility and dissolution rate. Complexation with cyclodextrin provided superior bioavailability than pure drug[13].

E) Alteration of pH of the drug microenvironment:

This can be achieved in two ways- in situ salt formation, and addition of buffers to the formulation e.g buffered aspirin tablets.

F) Precipitation:

In this method, the poorly aqueous soluble drug such as cyclosporine is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nano size particles. The product so prepared is also called as hydrosol.

G) Drug dispersion on carriers:

Selective Adsorption on Insoluble Carriers like bentonite can enhance the dissolution rate of poorly water soluble drugs by maintaining the concentration gradient at its maximum. The two reasons suggested for the rapid release of drugs from the surface of clays are- the weak physical bonding between the adsorbate, and hydration and swelling of the clay in the aqueous media. The adsorption of drug onto solid adsorbent may chances to reduce the rate and/or extent of drug absorption from the GIT[14].

A solid solution is a binary system comprising of a solid solute molecularly dispersed in a solid solvent. Since the two compartments crystallize together in a homogenous one phase system, solid solutions are also called as molecular dispersion or mixed crystals. In case of reduction in particle size to the molecular level, solid solutions show greater aqueous solubility and faster dissolution than eutectics and solid dispersion. They are generally prepared by fusion/melt method.

Eutectic mixture melts differ from solid solutions in that the fused melt of solute and solvent show complete miscibility but negligible solid-solid solubility, i.e., such systems are basically intimately blended physical mixture of two crystalline components.

Solid Dispersions[15] are generally prepared by solvent or co-precipitation method whereby both the guest solute and the solid evaporation carrier solvent are dissolved in a common volatile liquid solvent such as alcohol. The method is suitable for thermolabile substances but has a number of disadvantages like high cost of processing, use of large quantities of solvent, difficulty in complete removal of solvent.

II- Chemical Modification:

A) **Use of salt forms** has improved solubility and dissolution characteristics in comparison to the original drug. It is generally accepted that a minimum difference of 3 units between the pKa value of the group and that of its counter ion is required to form stable salts. Alkali metal salts of acidic drugs like penicillin's and strong acid salts of basic drugs like atropine are water-soluble than the parent drug.

B) **Soluble Prodrugs** are usually designed to improve oral bioavailability, with poor absorption from the gastrointestinal tract usually being the limiting factor.

1.4 Granulation[16]:

Granulation refers to the act or process in which primary powder particles are made to adhere to form larger as well as multiparticle entities. Granulation is one of the most important unit operations in the production of pharmaceutical oral dosage forms. However, there are many different technologies each having different strengths and weaknesses. The selection of

granulation type and method depends on drug properties. The method formation of granules are graphically shown below.

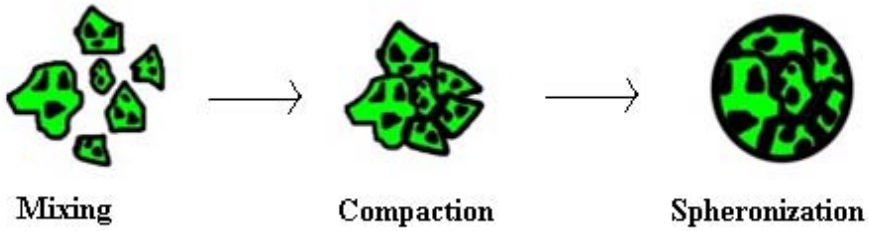


Fig.5 Steps involved in granulation

Reasons for granulation:

- To prevent the segregation of the constituents of powder mix. Segregation is due to differences in the size or density of the component of the mix.
- Granules form a cohesive system will be larger and more isodiametric, and also improve flow properties.
- Some powders are difficult to compact to rectify this problem by granulation to be employed.
- In case of powder have small size, irregular shape or surface characteristics, are cohesive and do not flow well.
- Granules are more stable against humidity and atmosphere and less likely to make cake or harden upon standing (less exposed surface area compared to powders).
- To improve the compression characteristics of the mixture and improve the appearance of the product.

GRANULATION MECHANISMS :

(A) PARTICLE-BONDING MECHANISMS

During granulation, particles adhere and agglomerate due to bond formation. These bonds should be strong enough to allow granules to withstand handling without breakdown.

(B) GRANULE GROWTH MECHANISMS

In the dry methods, particle adhesion takes place because of applied pressure. A compact or sheet is produced which is larger than the granule size required, and milling and sieving can attain therefore the required size. The compact masses are called as slugs, and the process is referred to as “slugging”.

In wet granulation methods, liquid added to dry powders has to be distributed through the powder by the mechanical agitation created in the granulator. Process of formation of granules by different steps like nucleation, transition and ball growth.

1.5. TYPES OF GRANULATION

Wet Granulation[17]

Wet granulation, the process of adding a liquid solution to powders, is one of the most common ways to granulate. It involves the massing of a mix of dry primary powder particles using a granulating fluid. The fluid contains a solvent which must be volatile so that it can be removed by drying, and be non-toxic. Typical liquids include water, ethanol and isopropanol either alone or in combination. The liquid solution can be either aqueous based or solvent based. The steps involved in the preparation of wet granules are graphically shown in Fig no: 6.

In case of dissolution, Wet granulation of poorly soluble drugs is more superior case than dry or other process. The process can be very simple or very complex depending on the characteristics of the powders, the final objective of tablet making, and the equipment that is available.

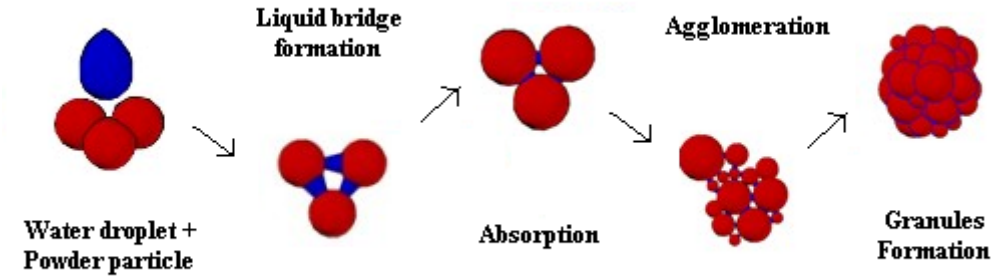


Fig.6 Steps involved in wet granulation process

Ultrafine powder may agglomerate spontaneously when agitated because of the bonding effect of vanderwaal's force and electrostatic forces[18]. In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules which are subsequently dried. The method of preparation of wet granulations by different methods like Fluid bed granulation, Pan granulation, Extrusion and palletizing, wet mass using rapid mixer granulator[19].

Dry Granulation[20]

The dry granulation process is used to form granules without using a liquid solution because the product to be granulated may be sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders. In this process the primary powder particles are aggregated under high pressure. The method of preparation of dry granulation by either roller compaction or slugging

Spray Granulation

The spray fluid bed granulator agglomerates finer particles into larger and free flowing. Ingredients are mixed and pre-heated by an upward flow of heated air. Granulation occurs by spraying liquid into the fluidized powder. The granules are subsequently dried with heated air. The top spray granulator can also be used for top spray coating, layering from liquids and instantizing.

Melt Granulation

In a melt granulation process, the binder solution of a standard wet granulation process is replaced with a meltable binder. This binder can be added in molten form, but the high shear process offers the benefit of allowing the binder to be added in its solid state. Melting is achieved by the energy added through the mixer fraction and the heated jacket of the bowl.

1.6. ORAL SOLID DOSAGE FORM[22]

The success of therapy depends on selection of appropriate delivery systems as much as it depends on drug itself. Oral solid dosage forms are the preferred routes for many drugs and are still the most widely used formulations for new and existing release products. Solid dosage forms include; powders, granules, tablets, capsules and suppositories.

Advantages of Oral solid dosage forms

- More stable than liquids, with longer expiration dates.
- Easy shipping and handling.
- Less needed shelf space.
- No preservation requirements.
- Accurate dosage (single dose).
- Suitable for sustained release preparation.

1.7. CAPSULE DOSAGE FORM[23]

Capsules are solid dosage form in which drug is enclosed within either a hard or soft container shell. Capsule refers to a range of techniques used to enclose medicines in a relatively stable shell. Hard gelatin capsule range from No.5, smallest to No.000, largest. Hard gelatin capsule consists of two, telescoping cap and body. The two main types of capsules are:

- Hard-shelled capsules, which are normally used for dry, powdered ingredients or miniature pellets. Hard gelatin capsules are more frequently filled with powders[24].
- Soft-shelled capsules, primarily used for oils and for active ingredients that are dissolved or suspended in oil.

Both of these classes of capsules are made from aqueous solutions of gelling agents like: Animal protein mainly gelatin or Plant polysaccharides or their derivatives like carrageenans and modified forms of starch and cellulose. Other ingredients can be added to the gelling agent solution like plasticizers such as glycerin and/or sorbitol to decrease the capsule's hardness, coloring agents, preservatives, disintegrants, lubricants and surface treatment[25].

Mechanism of Drug release from Capsule:

The steps involved in drug release from capsule shell are – after enter capsules in GIT fluid, swelling of capsule takes place, followed by capsule shell broken occur. Then the released drug undergoes solubility as well as dissolution occurs.

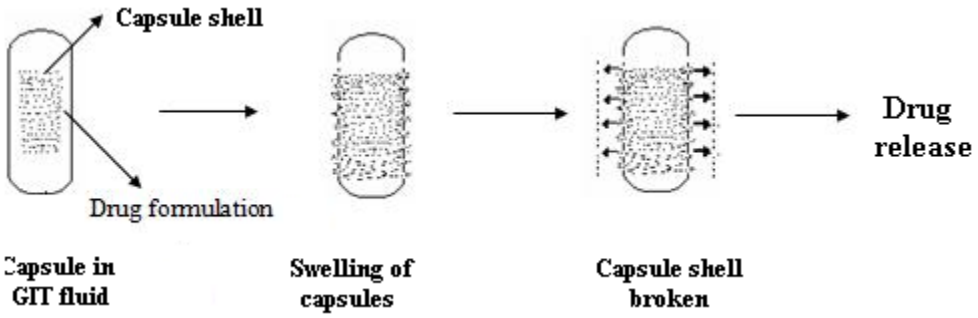


Fig.7 Mechanism of drug release from capsule shell

Pharmacokinetics of Drug release from capsules:

The pharmacokinetic of Drug release from capsules in immediate manner. The immediate release of drug from capsules was calculated using this equation:

$$\text{Immediate release} = \frac{Css \times Vd}{F}$$

Where, C_{ss} is steady-state plasma concentration (Avg. Cmax); V_d is volume of distribution; F is fractional bioavailability.

The total dose required for immediate release profile was calculated using this equation:

$$\text{Dose} = \text{Immediate release}\,[\,1 + (0.693 \times t/t50)$$

Where, t is time up to which controlled release is required; $t_{1/2}$ is half life of drug.

Advantage of Hard gelatin Capsule over other solid dosage form[26]:

- The bioavailability of solid dosage form to decrease in the order of capsule > tablet > coated tablet.
- A capsule dosage form should be quite efficient than other solid dosage form.
- The capsule contents should not be subjected to high compression forces which would tend to reduce the effective surface area, thus a capsule should perform better than a tablet.
- If a drug is hydrophobic a dispersing agent should be added to the capsule formulation, which minimize aggregation and maximize the surface area of the powder.
- The hard gelatin shell should disrupt rapidly and allow the contents to be mixed with the G-I tract contents.
- Reduces stability problem with sensitive drugs.
- Easy to swallow and improve patient compliances.

2. LITERATURE REVIEW

2.1. LITERATURE REVIEW ON DRUG:

Pamula bhavanam et al., 2010, studied formulation and evaluation of fenofibrate tablets using different binding agents were prepared by wet granulation method using sodium lauryl sulfate (SLS) and Povidone K-30 as a binding agents with different concentrations. The formulations were coded as Feno1 (SLS - 3%, PVP K-30 – 4%) Feno2 (SLS - 3%, PVP K-30 – 4%) and Feno3 (SLS - 3%, PVP K-30 – 4%). The formulated products were evaluated for uniformity of weight, friability, hardness, thickness, disintegration and dissolution. Among these formulations, F- 1 has more dissolution profile than other two formulations[27].

Ravi kumar et al., 2009, designed the formulation of mouth dissolving tablets of fenofibrate using sublimation technique by using different subliming agents like camphor, thymol, ammonium bicarbonate and different concentrations of menthol. Tablets with menthol at 12.5% concentration have shown quick disintegrating features. The *in vitro* drug release study revealed that menthol at a concentration of 12.5 % (F10) of the dosage form weight was able to fast the release of Fenofibrate within 10 minutes. Further optimized formulations (F10) were subjected to stability testing for 3 months at temperatures 25±5ºC/60±5%RH and 40±5ºC/75±5%RH. In conclusion, the results of this technique shows enhancement of the solubility and dissolution rate of poorly water-soluble drug like fenofibrate[28].

Ashok patel et al., 2007, formulated a SMEDDS (self-microemulsifying drug delivery system) of fenofibrate and evaluated the microemulsification existence area, and the release rate of fenofibrate by using Tween 80, PEG 400 in different concentration. The optimized formulation for in vitro dissolution and pharmacodynamic studies was composed of Labrafac CM10 (31.5%), Tween 80 (47.3%), and polyethylene glycol 400 (12.7%). The SMEDDS formulation can be used as a possible alternative to traditional oral formulations of fenofibrate to improve its bioavailability[29].

Pasut ratanabanangkoon et al., 2008, developed a novel formulation containing fenofibrate in omega-3-oil was developed using a novel throughput screening program. Different concentration of omega-3 oil, ethanol and sremophor EL and span 20. Emulsified formulation are prepared with 200nm by mild agitation.The optimized formulation Cremophor EL : Span 20 (50:50) tested

against the current marketed product Tricor in human healthy volunteers, the new formulation showed equivalent to Tricor[30].

Rajeev jain et al., 2008, studied the effect of powder processing on performance of fenofibrate formulations, in which powder blending and jet-milling were performed for the production of the bulk powders of 200-mg dose orally disintegrating tablets (ODTs) of fenofibrate. The bulk powders were granulated followed by blending and tableting. The materials were tested for DSC, drug particle sizing post-reconstitution, dissolution, optical micrography, SEM, X-ray Spectroscopy and disintegration of the ODTs. It was found that the crystallinity of fenofibrate was not impacted by the blending and jet-milling processes. Process A produced materials having poorer fenofibrate reconstitution as compared to processes involving jet-milling. It was discovered that milling a blend of fenofibrate/excipient (process C) was advantageous over milling the raw drug alone (process B). Process C yielded bulk powder that showed rapid dissolution and ODTs which exhibited rapid disintegration[31].

Liandong Hu et al., 2010, formulated a microemulsion for oral administration to improve the solubility and bioavailability of fenofibrate by using different ratios of oils, surfactants and co-surfactants (S&CoS) such as capryol, cremphore EL, transcutol. The formulations were characterized by solubility of the drug in the vehicles, mean droplet size, stability study and drug content. The optimal formulation consists of 25% Capryol 90, 27.75% Cremophore EL, Transcutol P 9.25% and water 38% (w/w), with a maximum solubility of fenofibrate up to ~40.96 mg/mL. The pharmacokinetic study was performed in dogs and compared with Lipanthy® capsule. The result showed that microemulsion has significantly increased the C_{max} and AUC compared to that of Lipanthy® capsule ($p< 0.05$). Results indicated that the microemulsions could be used as an effective formulation for enhancing the oral bioavailability of fenofibrate[32].

Ganesh et al., 2008, studied the dissolution rate of a poorly water-soluble drug, fenofibrate, is increased by adsorbing the drug onto silica. The adsorption is achieved by first dissolving the drug in supercritical carbon dioxide and then depressurizing the solution onto silica. Loadings of up to 27.5 wt % drug onto silica are obtained. The fenofibrate/silica formulation is free of any residual solvent, and carbon dioxide is freely removed upon depressurization. The formulation is characterized using IR, UV, X-ray diffraction, DSC and SEM. Based on *in vitro* dissolution study, a significant increase in the dissolution rate (~80% drug release in 20 min) of drug–silica

formulation is observed as compared to micronized fenofibrate (~20% drug release in 20 min), which can be attributed to increase in the surface area and decrease in the crystallinity of drug after adsorption onto silica. Two different formulations are compared: (A) amorphous fenofibrate/silica and (B) slightly crystalline fenofibrate/silica. The second formulation is found to be more stable on storage[33].

Zengrong Jia et al., 2011, formulated a novel solid particle system with a nanomatrix structure and without surfactant for the oral delivery of insoluble drugs was prepared. This used a combination of pH-sensitive polymethylacrylate and nano-porous silica, in order to improve the drug absorption using only pharmaceutical excipients and a relative simple process. The *invitro* drug dissolution and *invivo* oral bioavailability of this formulation, using fenofibrate as the model drug, were compared with other reference formulations such as a suspension, micronized formulation or self microemulsion drug delivery system (SMEDDS). The optimal formulation was evaluated by SEM, TEM, surface area analysis, DSC, and XRD. The optimized formulation prepared with polymethylacrylate (Eudragit®L100-55) and silica (Sylysia®350) markedly improved the drug dissolution compared with other reference preparations[34].

Yaping Chen et al., 2009, studied the oral bioavailability of the poorly water-soluble drug fenofibrate in liposomes containing a bile salt were used as oral drug delivery systems. Liposomes composed of soybean phosphotidylcholine (SPC) and sodium deoxycholate (SDC) were prepared by a dry-film dispersing method coupled with sonication and homogenization. *Invitro* release experiments indicated that no more than 20% of total fenofibrate was released from SPC/cholesterol (CL) and SPC/SDC liposomes at 2 h, in contrast with near complete release for micronized fenofibrate capsules. Strikingly, *invivo* measurements of pharmacokinetics and bioavailability demonstrated higher rates of fenofibrate absorption from both SPC/SDC and SPC/CL liposomes than micronized fenofibrate. The disparity between oral bioavailability and in vitro release for liposomes strongly suggests alternative absorption mechanisms rather than enhanced release. Importantly, SPC/SDC liposomes exhibited a 1.57-fold increase in bioavailability relative to SPC/CL liposomes, indicating that liposomes containing bile salts may be used to enhance oral bioavailability of poorly water-soluble drugs[35].

Markus Vogt et al., 2008, compared several techniques for improving the dissolution of fenofibrate, a poorly soluble drug. Particle size reduction was realized by jet milling (micronization; cogrinding with lactose, polyvinylpyrrolidone or sodium lauryl sulphate) and by

media milling using a bead mill (nanosizing) with subsequent spray-drying. Solid state characterization by X-ray diffraction and DSC method. Micronization of fenofibrate enhanced its dissolution rate in biorelevant media (8.2% in 30 min) compared to crude material (1.3% in 30 min). Coground mixtures of the drug increased the dissolution rate further (up to 20% in 30 min). Commercial products dissolved similarly to crude or micronized fenofibrate, but significantly slower than the coground or spray-dried fenofibrate mixtures. The results suggest that cogrinding and spray-drying are powerful techniques for the preparation of rapidly dissolving formulations of fenofibrate, and could potentially lead to improvements in the bioavailability of oral fenofibrate products[36].

Qiao-Ping Huang et al., 2009, studied the solidification process from emulsion, which consisted of emulsifier, water and molten drug as oil phase without use of any organic solvent, was firstly employed to prepare ultrafine fenofibrate (FF) powder. The effects of stirring speed and volume ratios of hot emulsion to cold water on the particle size and morphology were discussed as well as the impacts of different emulsifiers on emulsion. The produced ultrafine powder was characterized by SEM, XRD, FT-IR, specific surface area analysis and a dissolution test. The product had a mean particle size of about 3 μm & specific surface area reached up to 6.23 m^2/g, which were about 25 folds as large as that of bulk FF. In the dissolution tests, about 96.1% of ultrafine FF was dissolved after 120 min, while there was only 38.1% of bulk drug dissolved, proving that the dissolution property of ultrafine FF was significantly improved when compared to commercial drug[37].

Ming-Thau Sheu et al., 1994, designed the solid dispersion systems of the sparingly water soluble drug, fenofibrate in PEG 6000 and PVP were prepared and characterized. The effect of particle size of solid dispersions on the dissolution rate was also examined in ethanolic media at two stirring rates. An enhancing effect of increasing the proportion of PEG 6000 was achieved only for large particles when using a medium containing 60% ethanol with stirring at 100 rpm. However, in the same medium but with stirring at 50 rpm, the dissolution rate was reduced with the decreasing particle size. As expected, the decrease in drug solubility in the medium containing 40 or 50% of ethanol slowed down the dissolution rate of fenofibrate from the PEG 6000 solid dispersions, and the dissolution rate was also dependent on the particle size. The dissolution rate of fenofibrate from the physical mixture was slower than that from the solid

dispersion, and decreased with increasing proportion of PEG 6000 incorporated and with decreasing particle size. No evidence of a storage effect was obtained[38].

Srinarong et al., 2009, formulated the incorporation of superdisintegrants in solid dispersion tablets containing a highly lipophilic drug fenofibrate. In addition, the dissolution rate was more increased when the superdisintegrant was incorporated in the drug containing solid dispersions than when it was physically mixed with the solid dispersions. The dissolution rate enhancement strongly depended on the type of superdisintegrants and increased in the order Polyplasdone® XL-10 < Polyplasdone® XL <<Ac-Di-Sol® ≈ Primojel®. The dissolution behavior also depended on the type of hydrophilic carriers. Solid dispersion tablets based on inulin 4 kDa, polyethylene glycol and polyvinylpyrrolidone K30 showed a much faster dissolution than those based on mannitol and hydroxypropyl-β-cyclodextrin. Finally, inulin 4 kDa-based solid dispersion tablets showed excellent storage stability, while polyethylene glycol and polyvinylpyrrolidone K30-based solid dispersion tablets did not[39].

Vinayak et al., 2005, determined whether pH-sensitive polymeric micelles could improve the oral bioavailability of a poorly water-soluble drug. Poly(ethylene glycol)-*block*-poly(alkyl acrylate-*co*-methacrylic acid) used as ionizable polymer. Poorly water-soluble model drugs viz. fenofibrate (FNB) and progesterone (PRG) were incorporated in the self-assemblies by the oil-in-water emulsion or film casting methods. The pH-dependent release of several formulations was studied in vitro and the oral bioavailability of FNB-loaded micelles, Lipidil Micro® and FNB coarse suspension were assessed in Sprague–Dawley rats at a dose of 7.5 mg/kg. Entrapment efficiency ranged between 55–75% and was dependent on polymer composition and drug-loading method. Hydrophobic chain composition of the polymer had tremendous impact on in vitro release kinetics, with micelles showing the desired pH-dependent drug-release profile. The oral bioavailability of FNB from these self-assemblies revealed 156% and 15% increases vs. FNB coarse suspension and Lipidil Micro®, respectively. The results suggest that these pH-sensitive self-assemblies have potential for improving the oral bioavailability of poorly water-soluble drugs[40].

Michiel Van et al., 2010, studied the effect of release rate from ordered mesoporous silica materials on the rate and extent of absorption of the poorly soluble drug fenofibrate. Three ordered mesoporous silica materials with different pore diameter (7.3 nm, 4.4 nm and 2.7 nm) were synthesized and loaded with fenofibrate via impregnation. Release experiments were

conducted under sink conditions and under supersaturating conditions in biorelevant media, simulating the fasted and the fed state. The evaluation was observed *in vivo* (fasted state): the area under the plasma concentration–time profile amounted to 102 ± 34 μM h, 86 ± 19 μM h and 20 ± 13 μM h for the materials with pore diameter of 2.7 nm, 4.4 nm and 7.3 nm, respectively. The results of this, study demonstrate that a decrease in drug release rate – and thus, a decrease of the rate at which supersaturation is created – is beneficial to the absorption of fenofibrate[41].

2.2. LITERATURE REVIEW ON DOSAGE FORM:

Markus Vogt et al., 2008, studied the oral bioavailability of EMD 57033, a calcium sensitizing agent with poor solubility, was compared in dogs using four solid dosage form formulation approaches: a physical blend of the drug with excipients, micronization of the drug, preparation of coground mixtures and spray-drying of the drug from a nanocrystalline suspension. The formulations contained generally accepted excipients such as lactose, hydroxypropylmethyl cellulose and SLS in usual quantities. Drug micronization and cogrinding was realized by a jet-milling technique. All formulations were administered orally as dry powders in hard gelatine capsules. While micronization increased the absolute bioavailability of the solid drug significantly compared to crude material (from nondetectable to 20%), cogrinding with specific excipients was able to almost double this improvement (up to 39%). It was concluded that cogrinding can be a useful tool to improve the bioavailability of poorly soluble drugs from a solid dosage form format[42].

Xi Han et al., 2011, studied the simultaneous micronization and surface modification of drug particles e.g., to prevent - agglomeration, poor flowability, marginal increase in surface area and low bulk density. Particles of ibuprofen (102 μm), a model drug, pre-blended with hydrophilic nano-silica, are micronized down to 10 and 5 μm in a continuous fluid energy mill (FEM) to obtain fine surface modified particles. Significant improvement in flow properties and dissolution rate was observed when micronization accompanied surface modification. Additionally, co-grinding with water-soluble polymer during micronization led to further increase in bulk density and more enhanced dissolution rate improvement, which is attributed to improved wettability. XRD, DSC and Raman were used to examine crystallinity. The surface modified, micronized powders also showed improved dispersion, higher bulk densities (>0.4 g/ml), reduced electrostatic and higher flowability (FFC ≥ 6) compared to just micronized

powder (0.19 g/ml, FFC = 1.0), indicating they may be used in high drug loaded formulations amenable to direct compression[43].

Mohammed Barzegar et al., 2010, reported that gliclazide is practically insoluble in water, to improve the drug dissolution rate, cogrinding method was used as an approach to prepare gliclazide coground/solid dispersions (SDs) in the carriers such as povidone (PVP-K30), crospovidone and MCC (Avicel PH 101) with different drug to carrier ratios. The fastest dissolution rates were observed from coground formulations with the drug to carrier ratio of 1:5. The amount of drug dissolved in 15 min from these SDs was varied from 96% in the case of Avicel SD to 100% for SD of PVP. Whereas the amount of drug released in the same time from unground drug powder (UD), ground drug powder (GD) and all physical mixtures was between 60 and 80%. These results indicate that increased wettability and hydrophilicity of drug particles and deaggregation brought about by the carriers are the reasons for enhanced drug dissolution from the SDs. One of the possible advantages of formulating an insoluble drug such as gliclazide is that if it is used in preparation of capsules or tablets of the drug, its dose might be reduced which is economically beneficial[44].

S.W.Wong et al., 2006, predicted that surfactant helpful to improve the dissolution rate and subsequently the oral absorption and bioavailability of a model poorly water-soluble drug. Microparticles containing the model drug (griseofulvin) were produced by spray drying the drug in the absence/presence of a hydrophilic surfactant. Poloxamer 407 was chosen as the hydrophilic surfactant to improve the particle wetting and the dissolution rate. The results obtained showed that the dissolution rate and absolute oral bioavailability of the spray dried griseofulvin/Poloxamer 407 particles were significantly increased compared to the control. Although spray drying griseofulvin alone increased the drug's *invitro* dissolution rate, no significant improvement was seen in the absolute oral bioavailability when compared to the control. Therefore, it is believed that the better wetting characteristics conferred by the hydrophilic surfactant was responsible for the enhanced dissolution rate and absolute oral bioavailability of the model drug[45].

Markus Vogt et al., 2008, studied the rate of dissolution for four poorly soluble drugs (EMD 57033, albendazole, danazol and felodipine) was improved by cogrinding them with various excipients (lactose monohydrate, corn starch, PVP, HPMC and SLS) using a jet-milling technique. Solid state characterization studies by X-ray diffraction and differential scanning

calorimetry verified the maintenance of the crystalline state of the active substances after milling. In vitro dissolution of the coground mixtures in biorelevant media was much faster than from micronised drug in the corresponding physical mixtures for all four compounds. Cogrinding with lactose monohydrate resulted in fast dissolution with unstable supersaturation for EMD 57033. Cogrinding the same drug with PVP or HPMC produced a more sustained supersaturation. SLS accelerated the dissolution of EMD 50733 but inhibited supersaturation. The results suggest that the cogrinding with selected excipients is a powerful tool to accelerate the dissolution of poorly soluble drugs without converting the drug to the amorphous form or changing the particle size[46].

Stephen B Ruddy et al., 1999, formulated the feasibility of incorporating significant quantities of the anionic surfactant, sodium lauryl sulfate (SDS), MCC, mannitol into an immediate release tablet formulation of a poorly water-soluble immunosuppressive agent was investigated. Optimal in vitro release of the drug from the tablet formulation was achieved by establishing the minimum molar uptake ratio necessary to achieve complete micellar solubilization of the drug. A model-independent analysis of dissolution results in a reduced volume (250 ml) of modified simulated gastric fluid demonstrated that the rate and extent of drug release was highly dependent on the mean particle size of the bulk drug, but independent of compression force above that required to achieve a compact of acceptable mechanical strength. Employing the Korsmeyer–Peppas model of Fickian and non-Fickian drug release, it was further shown that release of the drug from the dosage form was governed largely by surface erosion of the surfactant-enriched tablet matrix[47].

G. K. Bolhuis et al., 1997, demonstrated that the dissolution from capsules and tablets of poorly soluble, hydrophobic drugs can be strongly improved by solid deposition of the drug upon hydrophilic, strongly swelling carriers like the super disintegrants sodium starch glycolate and croscarmellose sodium. As an effect of its lower swelling power, the super disintegrant crospovidone is far less effective than the other super disintegrants. Wet granulation of poorly soluble drugs with high concentrations of sodium starch glycolate resulted likewise in a strongly improved drug release and bioavailability from capsules and tablets. It was found, however, that granules containing a too high concentration of the super disintegrant slow down the drug release from tablets. This effect is caused by the formation of a viscous barrier of the super disintegrant in the granules during the dissolution process[48].

Akio Miwa et al., 2000, predicted the amounts of water addition suitable for pharmaceutical formulations in wet granulation, using a high-speed mixer or a fluidized bed granulator, before granulation trials. In order to determine the suitable amount of water, infrared moisture sensor (IR sensor) used to measure the amount of water at the powder surface. Further by analysis the plot (output value of the IR sensor vs. amount of added water) for each excipient, the amount of water addition for granulation was determined for it. As a second step, two model formulations were designed and suitable amounts of water for mixer granulation. Suggested that the above method is useful for estimating suitable amounts of addition of water for formulations before granulation trials.granulation were predicted by summation of the obtained excipient values. The predicted value was compared with the experimental value for high-speed[49].

Beatrice albertini et al., 2003, investigated the use of different excipients, β-lactose and polyvinylpyrrolidone of two molecular weights (PVP K12 and PVP K90), in the production of improved release piroxicam granules, by wet granulation using water and steam as granulation liquid. The formulations examined were: piroxicam (Px)/β-lactose; Px/PVP K12 and Px/PVP K90, each one at a 1:9 weight ratio. Image analysis revealed that β-lactose steam granules had a larger surface area with respect to water granules, whereas lower values of this parameter were observed in PVP-s granules, confirming the SEM and the fractal analysis results. As regards the enhancement of the dissolution profiles, the best result was obtained using β-lactose steam granules followed by PVP K12. DSC analysis suggested the partial amorphisation of the drug in the granules containing the three excipients. This result was then confirmed by X-ray powder diffraction. Therefore, β-lactose and PVP K12 could be proposed as useful excipients to enhance the dissolution rate of Px from granules prepared using the granulation technique[50].

Kreutzwald et al., 2007, studied the effect of diluents and disintegrants on the release of poorly soluble drugs from hard gelatin capsules. The release of poorly soluble spironolactone depended on the solubility of diluents. Dissolution of drug from lactose-based capsules has been observed to be pH dependent. Release of spironolactone from microcrystalline cellulose-based capsules was similar at pH2 and 6.8. The effect of disintegrant is highly dependent on the physicochemical properties of diluents. Release of spirolactone from Verospiron was slower than that from lactose-based and microcrystalline based capsules prepared[51].

Ojantakanen et al., 1993, studied the effect of viscosity grade of the polymer diluent on the bioavailability of ibuprofen from hard gelatin capsules was evaluated in two single-dose (400

mg) cross-over studies in healthy volunteers. The polymers studied were HPMC K100 and K15M, and NaCMC (LV, MV and HV). Plain ibuprofen capsules were used for reference. Use of HPMC K15M led to sustained drug absorption from the capsules. The t_{max} and C_{max} values differed significantly ($P < 0.001$) from the reference values. The sustaining effect of the lower viscosity grade, K 100, was less pronounced. NaCMC-based capsules exhibited sustained-release properties similar to those of the HPMC K 100 capsules. In the case of NaCMC, the molecular weight of the polymer had no significant effect on drug absorption. No differences in the extent of bioavailability of ibuprofen between the formulations studied[52].

Guyot et al., 1996, formulated as a cross-linked with terephtaloyle chloride before being filled with pure theophylline powder. The in vitro drug release was carried out on comparison with conventional HGC - Dilatrane®. Release profiles showed that cross-linking before or after drying of capsules allowed sustained release of drug. The rate of release decreased when the cross-linking reaction time was increased. When the reaction time was of 30 min, capsules exhibited a nearly zero-order release ($r = 0.999$) with a cumulative drug release of 63.24 ± 10.48% only. Cumulative drug release, $DT_{50\%}$ and DE from capsules cross-linked before drying had nearly the same release characteristics as Dilatrane®[53].

Ambrus et al., 2007, studied the poor aqueous solubility of nifluminic acid (NIF), to improve its solubility and dissolution rate through the preparation of formulations based on hydroxypropyl β-cyclodextrin (HPβCD) and polyvinylpyrrolidone K25 (PVP K25), a combination of carriers which has been advantageously used for a similar purpose with various hydrophobic drugs. Ternary systems of NIF, HPβCD, and PVP K25 were prepared in different drug of CD to PVP ratios by physical mixing, kneading, microwave irradiation, and co-evaporation. Differential scanning calorimetry, thermogravimetric analysis, hot stage microscopy, Fourier transform infrared spectroscopy, and X-ray powder diffractometry were used to investigate the resulting solid-state interactions. The results showed that the solid state of the drug in the amorphous or crystalline ternary combinations of CD to PVP (6:4) influenced both the solubility and the dissolution rate of NIF[54].

Badawi A et al., 2011, formulated Itraconazole (ITZ) by a simple solid dispersion method (melt method). Binary and ternary ITZ systems were prepared using different polymers including crystallization inhibiting polymers (Pluronic F68, Pluronic F127, Eudragit EPO and PVP K25) at different ratios. The prepared solid dispersions of itraconazole were characterized by DSC, X-

Ray diffraction and infrared spectroscopy. All of the prepared systems showed faster and higher dissolution rates compared to raw and glassy ITZ. Stability studies of selected systems demonstrated that the itraconazole/Pluronic F127/Eduragit EPO (1:1:0.5), T6 ternary system was chemically (absence of degradation products) and physically stable (stable dissolution rate and negligible change in drug crystallinity) after three months of storage under different conditions[55].

Ahuja et al., 2007, formulated the solid dispersions of rofecoxib with PVP K-25, PEG4000 and PEG 6000 in 50%, 75% and 90%w/w were prepared by hot-melt method. The solubility efficiency of polymers was in the order of PVP >> PEG 4000 > PEG 6000 due to high amorphizing properties of PVP than the PEGs. Significant dissolution improvement was observed at the highest carrier amount i.e. 90% and was ascribed to the formation of interstitial solid solutions. Drug with PVP K-25 shows better dissolution profile than with other polymer. Concluded that, PVP K-25 is better choice for poorly soluble drugs[56].

Sherif IF et al., 2006, Studied the Effect of Wet Granulation on Microcrystalline Cellulose Particle Structure and Performance by using MCC alone and with hydroxypropyl cellulose (HPC) as a binder were wet granulated by a high-shear process. Result shows decrease in MCC compatibility after granulation and also decrease in MCC primary particle porosity and in some cases with the formation of large dense granules as well. Effect of milling seems to counteract the effect of wet granulation on MCC compatibility[57].

Guo M et al., 2003, Designed to evaluate and compare SMCC's performance to that of other excipients commonly used in hard gelatin capsule direct-fill formulations. Four grades of SMCC, Anhydrous lactose (direct tableting grade), pregelatinized starch (PGS) (Starch 1500), and microcrystalline cellulose (MCC) (Emcocel 90M) were chosen as the control fillers. The presence of colloidal silicon dioxide in SMCC not influences the dissolution of these drugs. It shows that SMCC could be a suitable direct-fill excipient for hard shell capsule formulations[58].

Simon M et al., 2001, studied Nucleation, growth and breakage phenomena in agitated wet granulation processes and also evaluated. Particular emphasis on the fact exist. And also explained the majority of experimentally observed behavior of particle rheology. The data suggests the formulation properties that control granulation behaviour, such as contact angle and dynamic yield strength[59].

Pathak N et al., 2011, undergone the process optimization research for Disulfiram immediate release tablet by dry granulation technique using different fillers, disintegrant and lubrication. Poor flow property shown in the formulation with less concentration of Colloidal Silicon Dioxide. In the addition of constant concentration of Colloidal Silicon Dioxide shows improved flow property and absence of static charges during slugging[60].

Limin shi et al., 2011, determined the evolution of powder tabletability and flowability during wetting and nucleation stages of high-shear wet granulation process. Forty-five percent of water led to more particle rounding and commencement of nucleation, which impacted tabletability and flowability. Enhanced powder flowability achieved by surface smoothing with granule rounding as a minor contributor[61].

Biljana G et al., 2011, Investigated to improve the mechanical strength of Paracetamol tablet as direct compression. From this study found out the effect of Polyplasdone® XL-10 shows faster disintegration time and dissolution rate in comparison with other polymers. Incase of results, usage of polyplasdone XL-10 particles is beneficial for the manufacturing of tablets with immediate release[62].

Suhas M K et al., 2010, studied losartan potassium to achieve a better dissolution rate and further improving the bioavailability by mouth dissolving tablets. Formulated using Polyplasdone XL 10, Croscarmellose sodium and Explotab in different concentration and evaluated. Among these formulations with 5%w/w Polyplasdone XL 10 release up to 99.26% within 12 min shows best results[63].

Venkata ramana., 2009, undergone the research to develop oral disintegrating tablet amlodipine besylate using Mannitol, sodium lauryl Sulphate, Aspartame and Acesulfamate used to cosifting and serial of blending with other excipients. All the formulation shows low weight different disintegration time and rapid in vitro dissolution. The results revealed that the enhanced wetting property with addition of SLS and shows faster release profile[64].

Preetha et al., 1998, studied the effect of mode of incorporation of different superdisintegrants like croscarmellose sodium, sodium starch glycolate and crospovidone in different soluble drugs. All the tablets prepared by wet granulation method. The study reveals that extragranular mode of addition seemed to be the best mode of incorporation and improved dissolution profile of the formulation[65].

Garry et al., 1997, Investigated the physiological significance of the *invitro* drug-excipient interaction between croscarmellose sodium NF and weakly basic drugs. In three formulations not used starch and Croscarmellose in control, starch alone, Starch & croscarmallose sodium. The result shows from the 6 healthy volunteers CONTROL, 22.94 mg; STARCH, 22.41 mg; CROS, 22.85 mg[66].

Ferrero et al., 2010, Predicted the efficiency of croscarmellose sodium in a direct compression formulation containing a poorly water soluble drug. The shortest disintegration time shows the mixtures more prone to plastic deformation and densification at same level of applied pressure and revealed a finer pore structure. As a result found that the disintegration response in tablets formulated with a disintegrant mainly acting by swelling mechanism[67].

Nagasamy V et al., 2006, designed to develop and evaluate sustained release matrix tablets of prochlorperazine maleate using HPMC, carbopol and combination of polymers by wet granulation technique. The flow and compression characteristics of the prepared granules significantly improved by virtue of wet granulation process. Mathematical analysis of the release kinetics indicated the nature of the drug release from the matrix tablets by wet granulation method obeying first order kinetics[68].

Graham B et al., 2009, studied the properties of amorphous materials and its manufacture, storage and use of medicines. HyperDSC was such that the glass transition (*T*g) of polyvinylpyrrolidone could be detected in granules and show realistic levels of this binder. The result shows that the dissolution of some lactose and that the amorphous binder holding the granules together is in fact a solid dispersion. From this study concluded that amorphous particle has more stability[69].

Yadhav et al., 2011, Investigated the study to develop a compaction technique to enhance the solubility, dissolution rate and other physicochemical properties of poorly water-soluble drugs using different polymers like HPMC, Kollicoat IR, Chitosan, PolyvinylPyrrolidone. The mechanism for dissolution enhancement is believed to be a microenvironment polymer surfactant effect facilitated by keeping the PVP polymers shows better drug dissolution[70].

James D et al., 2011, investigated the binder addition method, affects the growth and properties of granules. And also compared the binder distribution using alternative addition methods in both high shear mixer and fluidised bed. The result shows that the binder distribution by mass is also

investigated and also shows higher binder content in the larger size classes. The majority of binder can instead be found around the mean size of the batch[71].

Chowdary et al., 2011, predicted the method to develop nimesulide rapidly dissolving tablet formulations by wet granulation and direct compression methods. Nimesulide rapidly dissolving tablets with >85% dissolution in 30 min could be formulated employing starch phosphate as directly compressible and also with nimesulide-starch phosphate as (1 : 2) solid dispersion by wet granulation method shows better biowaiver[72].

Vikas A S et al., 2009, reviewed for complete absorption and good bioavailability of orally administered drug and it must be dissolved in gastric fluids. Studied improving solubility and dissolution rate by using Polymers, super disintegrants, surfactants are extensively supported dissolution enhancement in drugs. The drug with disintegrant and surfactant improves the dissolution profile with quicker solubility in gastric fluid[73].

Karen P H et al., 2009, studied the Granulation of hydrophobic powders and its structural complexity of new drug molecules. And also studied the wetting and spreading of the fluid through the powder particles is a prerequisite for good granulation. The hollow granule structure suggests the possibility of using the controlled, open granule structure to manufacture designer structured agglomerates with advantageous properties. Research results and observations shows that granules are a preliminary framework for liquid marble formation[74].

Musa et al., 2008, studied the intimate physical association between chitosan and silica in immediate release formulation. It shows water uptake, water saturation for gelling formation, and compactability among other superdisintegrants. Results have shown that chitosan–silica delivers superior performance in wet granulation formulation as a disintegrant[75].

Jen sen wu et al., 2001, investigated effect of codried product of microcrystalline cellulose (MCC) with b-cyclodextrin (b-CD) in wet granulation method and effect of lubrication. The codried products were lubricated with magnesium stearate in three different percentages (0.2, 0.5, and 1.0%). The result shows that codried product and Avicels were sensitive to lubrication and resulted in decreasing compactibility and increasing disintegration[76].

3.1. AIM OF WORK

An antilipemic agent, fenofibrate decreases the levels of fatty substances in the blood. Fenofibrate compound belongs to BCS-II classification (drug with very low solubility and has high lipophilicity). Dissolution rate of fenofibrate is expected to limit its absorption from GIT. Three major approaches available to overcome the bioavailability problem like pharmaceutic, pharmacokinetic and biologic approaches. In the objective of present study to enhance dissolution of fenofibrate by pharmaceutic method with different approaches like:

First approach: Micronization by using jet milling with different cycle process such as 1-cycle, 2-cycle, 3-cycle.

Second approach: Optimize the best binding agent from their different concentration

Third approach: Fix the suitable concentration of surfactant for formulation based on the study of extra-granular and intra-granular incorporation.

Fourth approach: Choose the quantity of binder solution use to get the effective formulation.

Also monitor the different parameters involved in wet granulation process, drying steps and capsule filling process.

Our ultimate goal is to enhance the dissolution profile of poorly soluble drug, fenofibrate with simple manufacturing process, lower cost effective, more bioavailability, standard quality and higher stability.

3.2. PLAN OF WORK

The research plan was carried out in the following stages:

- Micronization of fenofibrate by using jet milling in air pressure with different cycle process such as 1-cycle, 2-cycle, 3-cycle.

- Preformulation studies of micronized fenofibrate with different formulation excipients to assess their interaction with the drug and stability of the drug to select suitable excipients.

- Development of suitable formulation for micronized fenofibrate by using the selected excipients and selected solubility enhancement methods.

- Evaluation of Process parameters such as Physical characterization, Weight variation, Uniformity content, Disintegration, Cap lock length, Dissolution and Similarity factor along with study release characteristics of developed oral solid dosage form.

- An optimized formulation showing desired release profile would be selected and stability studies would be carried out according to the regulatory guidelines.

4. LIST OF MATERIALS AND INSTRUMENTS

4.1. MATERIALS USED

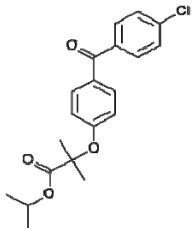
S.No:	MATERIALS	NAME OF THE MANUFACTURER
1.	Fenofibrate	Harman Finochem, Mumbai.
2.	Microcrystalline cellulose (Avicel pH – 101)	FMC Biopolymers, U.S.A
3.	Unipure Starch – F	National Starch LLC, Thailand.
4.	Croscarmellose sodium (Ac-Di-Sol)	FMC Biopolymers, U.S.A.
5.	Polyplasdone XL-10	ISP Sales Corp., U.K.
6.	Sodium Lauryl Sulfate	Stepan Co, U.S.A.
7.	Poly Vinyl Pyrollidine (PVP K-25)	ISP Sales Corp., U.K.
8.	Colloidal silicon dioxide	FMC Biopolymers, U.S.A.
9.	Talc	Luzenac Pharma, France.
10.	Magnesium Stearate	Merck Pharmaceuticals, France.
11.	Purified water	Millipore purified, India.

4.2. INSTRUMENTS USED

S.No:	INSTRUMENTS	NAME OF THE MANUFACTURER
1.	Single pan Electronic balance	Ax, Shimadzu – corporation, Japan
2.	pH meter	Mitler Talido, Switzerland
3.	Jet mill	Alpine 50 AS, Japan
4.	FT IR- 8400	Shimadzu Corporation, Kyoto, Japan
5.	Tap density apparatus	Electro Lab ETD – 1020, India.
6.	LOD Apparatus	Sartorius, Germany
7.	UV spectrophotometer1601	Shimadzu – corporation, Japan
8.	X-ray diffractometer	Philips PW3710, Japan
9.	Particle size analyzer	Malvern, UK
10.	Surface area analyzer	Microtrac, US
11.	Melting point apparatus 100	Stanford Research Systems, Inc. US
12.	Rapid mixer granulator	S. K. Pharma, India
13.	Fluidized bed dryer	S. K. Pharma, India
14.	Capsule filling machine	Pankaj industries, India
15.	Particle size distribution	Malvern, UK
16.	Vernier calipers	Mitutoyo corps, Japan
17.	Dissolution apparatus	TDT – 08L, Electrolab, India.
18.	Stability chamber	Osworld, Mumbai, India.
19.	DSC analyser-821	Mettler-toledo, Switzerland

5.1 DRUG PROFILE

MOLECULAR STRUCTURE OF FENOFIBRATE:



IUPAC NAME:

Propan-2-yl,2-{4-[(4-chlorophenyl)carbonyl]phenoxy}-2-methylpropanoate

FENOFIBRATE IDENTIFIERS:

CAS number: 49562-28-9

Drug Bank: APRD00405

Category: Anti-Hyperlipidemic

Bio Pharmaceutical Classification System: Class-II

CHEMICAL DATA:

Formula: $\mathbf{C_{20}H_{21}NCLO_4}$

Mol. Mass: 360.831 g/mol

Solubility: Less soluble in water

DESCRIPTION:

Fenofibrate is a drug of the fibrate class. Fenofibrate was developed by Groupe Fournier SA. It is mainly used to reduce cholesterol levels in patients at risk of cardiovascular disease. Like other fibrates, it reduces both low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels, as well as increasing high-density lipoprotein (HDL) levels and

reducing triglycerides level. It also appears to have a beneficial effect on the insulin resistance featured by the metabolic syndrome. It is used alone or in conjunction with statins in the treatment of hypercholesterolemia and hypertriglyceridemia.

PHARMACOKINETIC DATA:

Absorption

The absolute bioavailability of Fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, Fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled Fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration.

Distribution

Upon multiple dosing of Fenofibrate, fenofibric acid steady-state is achieved within 9 days. Plasma concentrations of fenofibric acid at steady-state are approximately double those following a single dose. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, Fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged Fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither Fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, Fenofibrate is mainly excreted in urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled Fenofibrate, approximately 60% of the dose appeared in urine and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

MECHANISM OF ACTION:

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of peroxisome proliferator-activated receptor type alpha (PPARα). Through activation of PPARα fenofibrate increases the lipolysis and elimination of atherogenic triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII.

TREATMENT FOR CHOLESTEROL DEPOSITION:

The mode of action in case of cholesterol deposition in patients by activation of PPARα also induces an increase in the synthesis of apoproteins AI and AII, which leads to a reduction in very low- and low-density fractions (VLDL and LDL) containing apoprotein B and an increase in the high-density lipoprotein fraction (HDL) containing apoprotein AI and AII. In addition, through modulation of the synthesis and catabolism of VLDL fractions, fenofibrate increases the LDL clearance and reduces small and dense LDL, the levels of which are elevated in the atherogenic lipoprotein phenotype, a common disorder in patients at risk for coronary heart disease.

OTHER USES:

- Fenofibrate has a uricosuric effect
- Making it of use in the management of gout.
- It also acts as a blood thinner by lowering the amount of fibrinogen in the blood

SIDE EFFECTS:

Minor effects like: Headache; nausea. Severe allergic reactions in over dosage condition like (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); calf pain; chest pain; confusion; dark urine; fast, slow, or irregular heartbeat; fever, chills, or persistent sore throat; increased coughing or coughing up blood; muscle pain, tenderness, or weakness (with or without fever and fatigue); pale stools; red, swollen, blistered, or peeling skin; severe or persistent dizziness or lightheadedness; severe or persistent nausea, stomach pain, or vomiting; severe pain or swelling in the ankles, feet, or legs; shortness of breath; unusual bruising or bleeding; yellowing of the skin or eyes.

DRUG INTERACTIONS:

The following drugs can interact with fenofibrate:

- A blood thinner such as warfarin (Coumadin);
- Cyclosporine (Neoral, Sandimmune, Gengraf);
- Other cholesterol-lowering medicines such as lovastatin (Mevacor), simvastatin (Zocor), pravastatin (Pravachol), fluvastatin (Lescol), atorvastatin (Lipitor), or cerivastatin (Baycol).

CONTRAINDICATION:

Fenofibrate is contra-indicated in children, during pregnancy or lactation, in patients with liver insufficiency, presence of gallstones, renal insufficiency, in patients hypersensitive to fenofibrate and/or excipients, known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen

PREGNANCY AND LACTATION:

Fenofibrate has been assigned to pregnancy category C by the FDA. Animal reproductive studies with doses 7 to 10 times the recommended human dosage based on body surface area (BSA) have demonstrated embryocidal and teratogenic effects. There are no controlled data in

human pregnancy. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Animal studies have revealed a potential for tumorigenicity, so considers the use of fenofibrate contraindicated in nursing women

FORMULATIONS:

All fenofibrate formulations are available as solid dosage form. It is under the brand name Tricor and Trilipix by Abbott Labs, Lipofen by Kowa Pharmaceuticals America Inc, Lofibra by Teva, Lipanthyl, Lipidil, and Supralip by Solvay Pharmaceutical, Fenocor-67 by Ordain Health Care, Fenogal by SMB Laboratories, Antara by Oscient Pharmaceuticals, and Golip by GolgiUSA.

COMBINATION WITH OTHER DRUGS:

Fenofibrate combination with atorvastatin, shows an increase in the high-density lipoprotein fraction (HDL) containing apoprotein AI and AII. It available in brand name as (Dyslip, Dysliptin, Atorin,etc.). Other combinational drugs with fenofibrate are Fluvastatin + fenofibrate, Allicin + Fenofibrate, Rosuvastatin + Fenofibrate, Etc.

7. EXCIPIENTS PROFILE

7.1. MICRO-CRYSTALLINE CELLULOSE:

Non-proprietary names:

BP: Micro crystalline cellulose; JP: Micro crystalline cellulose; PhEur: Cellulosum microcrystalanium; USPNF: Micro crystalline cellulose

Synonyms:

Avicel PH101, Celex, Cellulose gel, Celphere, Ceolus KG, crystalline Cellulose, E460, Emcocel, Ethispheres, Fibrocel, Pharmacel, Tabulose, Vivapur.

Chemical name: Cellulose

Empirical Formula: $(C_6H_{10}O_5)$ n Where n=220 Molecular weight 36000

Functional category:

Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant

Application in Pharmaceutical formulation or technology:

Micro crystalline cellulose pH 101 is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. In addition to its use as a binder/diluent, micro crystalline cellulose pH 101 also has some lubricant and disintegrant properties that make it useful in tableting.

Table:1 Uses of Microcrystalline cellulose

Use	Concentration (% w/w)
Anti adherent	5-20
Capsule binder/diluent	20-90
Tablet disintegrant	5-15

Description:

Micro crystalline cellulose pH 101 is purified, partially depolymerised cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. Its commercially available in different particle sizes and moisture grades that have different properties and applications.

Solubility:

Slightly soluble in 5 % w/v sodium hydroxide solution, practically insoluble in water, dilute acids, and most organic solvents.

7.2. CROSCARMELLOSE SODIUM:

Synonyms:

Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

Empirical Formula:

Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium.

Functional Category:

Tablet and capsule disintegrant.

Application:

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant. In tablet formulations, croscarmellose sodium may be used in both direct-compression as well as wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extra granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet granulation process.

Table:2 Uses of Croscarmellose Sodium

Use	Concentration (%)
Disintegrant of capsules	10-25
Disintegrant in tablet	0.5–5.0

Description:

Croscarmellose sodium occurs as an odorless, white or grayish-white powder.

Acidity/alkalinity: pH = 5.0–7.0 in aqueous dispersions.

Density (bulk): 0.529 g/ cm^3 for Ac-Di-Sol

Density (tapped): 0.819 g/ cm^3 for Ac-Di-Sol

Density (true): 1.543 g/ cm^3 for Ac-Di-Sol

Particle Size Distribution:

- Ac-Di-Sol: not more than 2% retained on a #200 mesh and not more than 10% retained on a #325 mesh.
- Pharmacel XL: more than 90% less than 45 μm, and more than 98% less than100 μm in size.

Solubility:

Insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times on contact with water. Practically insoluble in acetone, ethanol and toluene.

Stability and Storage Conditions:

Croscarmellose sodium is a stable though hygroscopic material. A Tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, no significant difference in drug dissolution after storage at 30°C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool and dry places.

Incompatibilities:

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminium, mercury, and zinc.

Method of Manufacture:

Alkali cellulose is prepared by steeping cellulose, obtained from wood pulp or cotton fibres, in sodium hydroxide solution. The alkali cellulose is then reacted with sodium monochloroacetate to obtain carboxymethylcellulose sodium. After the substitution reaction is completed and all of the sodium hydroxide has been used, the excess sodium monochloroacetate slowly hydrolyzes to glycolic acid. The glycolic acid changes a few of the sodium carboxymethyl groups to the free acid and catalyzes the formation of crosslinks to produce croscarmellose sodium. The croscarmellose sodium is then extracted with aqueous alcohol and any remaining sodium chloride or sodium glycolate is removed. After purification, croscarmellose sodium of purity greater than 99.5% is obtained. The croscarmellose sodium may be milled to break the polymer fibers into shorter lengths and hence improve its flow properties.

Safety:

Croscarmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially non-toxic and non-irritant material. Oral consumption of large amounts of croscarmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems.

7.3. CROSPOVIDONE:

Crospovidone XL-10 is a cross linked homo polymer of 1- ethenyl pyrrolidin-10-one. Its available in different degrees of powder fineness.

Molecular formula: $(C_6 H_9 NO)_n$

Description: Hygroscopic, White or yellowish white powder.

Bulk Density: 0.24 – 0.28 gm / cm^3

True Density: 0.35 – 0.45 gm / cm^3

Solubility: Practically insoluble in water, in alcohol and in methylene chloride.

Stability and storage condition:

Crospovidone is a stable and should be stored in a well closed container in a cool and dry place.

Incompatibilities:

Crospovidone is incompatible with most organic and inorganic pharmaceutical ingredients. When exposed to high water levels, crospovidone may form molecular adducts with some materials.

Handling precautions:

Eye protection, glove and a dust mask are recommended.

Uses:

Crospovidone is used in oral pharmaceutical formulation as a disintegrants for capsules, tablets and granules.

7.4. STARCH:

Synonyms: Unipure-F; cassava starch; fluftex W; melojel; paygel 55; pure-dent; tablet white.

Description:

It occurs as an odorless and tasteless, fine, white-colored powder comprised of very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

Functional category:

Glidant; tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

Solubility:

Practically insoluble in cold ethanol 95%, and cold water.

pH: 5.5-6.5

Density (bulk): 0.462 gm/cm^3

Density (tapped): 0.658gm/cm^3

Moisture content:

All starches are hygroscopic and rapidly absorb atmospheric moisture

Stability and storage condition:

Dry, unheated starch is stable if protected from high humidity. When used as a diluent or disintegrant in solid dosage forms, starch is considered to be inert under normal storage conditions.

Incompatibilities: Nil

Safety:

It is widely used as an excipient in pharmaceutical formulations, particularly oral tablets. It is an edible food substance and is generally regarded as an essentially nontoxic and nonirritant material.

Applications:

It is widely used as an excipients primarily in oral dosage formulations where it is utilized as a binder diluent and disintegrant. In tablet formulations, freshly prepared starch paste is used at a concentration of 5-25% w/w in tablet granulations as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration rate and drug dissolution rate. It is one of the most commonly used tablet disintegrants at concentrations of 3-15% w/w.

7.5. PURIFIED TALC:

Synonyms: Hydrous magnesium calcium silicate.

Chemical Name: Talc.

Empirical Formula: Approximate $Mg_6(Si_2O_5)_4(OH)_4$

Functional Category:

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Application in Pharmaceutical Formulation:

Table:3 Uses of Purified Talc

Use	Concentration (%)
Dusting powder	90.0–99.0
Glidant and tablet lubricant	1.0–10.0
Tablet and capsule diluent	5.0–30.0

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent. It is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release

pellets; and as an adsorbent. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Description:

Talc is very fine, white to greyish white, odorless, impalpable, crystalline powder. It adheres readily to skin and soft to touch and free from grittiness.

pH: 7-9.

Solubility:

Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Stability and Storage:

Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibility:

It is incompatible with quaternary ammonium compounds.

7.6. MAGNESIUM STEARATE:

Synonyms: Magnesium octadecanoate, Octadecanoic acid, Stearic acid.

Empirical Formula: $C_{36}H_{7O}MgO_4$.

Molecular Weight: 591.34.

Application in Pharmaceutical Formulation:

Primarily used as lubricant in capsule and tablet at a concentration between 0.25% - 5.0% w/w.

Description:

Magnesium stearate is very fine, light white, precipitated or milled impalpable powder of low bulk density having a faint order of stearic acid and characteristic taste. The powder is greasy to touch and readily adheres to skin.

Magnesium stearate is hydrophobic and may retard the dissolution of a drug from a solid dosage form; the lowest possible concentration is therefore used in such formulations. Capsule dissolution is also sensitive to both the amount of magnesium stearate in the formulation and the mixing time; higher levels of magnesium stearate and long mixing times can result in the formation of hydrophobic powder beds that do not disperse after the capsule shell dissolves.

An increase in the coefficient of variation of mixing and a decrease in the dissolution rate have been observed following blending of magnesium stearate with a tablet granulation. Tablet dissolution rate and crushing strength decreased as the time of blending increased and magnesium stearate may also increase tablet friability. Blending times with magnesium stearate should therefore be carefully controlled.

Loss on Drying: ≤6.0%.

Solubility:

Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Incompatibility:

Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in product containing aspirin, some vitamins and most alkaloidal salts.

7.7. SODIUM LAURYL SULFATE (SLS):

Synonyms: Sodium octadecyl sulfate, Sodium deodecanesulfate.

Empirical Formula: $NaC_{12}H_{25}SO_4$;

Molecular Weight: 288.38 g mol^{-1}

Density: 1.01 g/cm^3

Melting Point: 206^0C

Production of SLS:

SLS is synthesized by treating lauryl alcohol with sulfur trioxide gas, or oleum, or chlorosulfuric acid to produce hydrogen lauryl sulfate. The industrially practiced method typically uses sulfur trioxide gas. The resulting product is then neutralized through the addition of sodium hydroxide or sodium carbonate.

Application in Pharmaceutical Formulation:

SLS is used to improve the solubility of lipophilic drugs. Sodium lauryl sulfate is used rectally as laxative in enemas, and as an excipient on some dissolvable aspirins and other fiber therapy caplets. SLS is mainly used in detergents for laundry and many clearning applications. SLS is a highly effective surfactant and is used in any task requiring the removal of oily stains and residues. For example, it is found in higher concentrations with industrial products including engine degreasers, floor cleaners, and car wash soaps. It is found in toothpastes, shampoos, shaving foams, and bubble bath formulations in part for its thickening effect and its ability to create a lather.

Incompatibility:

Sodium lauryl sulfate diminishes perception of sweetness. Its more sensitivity, large usage results in aphthous ulcer.

7.8. POLY VINYL PYRROLIDINE:

Synonyms: PVP, Povidone, Polyvidone, Different grades like K-25, K-30, K-90.

Empirical Formula: $(C_6H_9NO)_n$;

Molecular Mass: 2500 - 25000 g mol^{-1}

Density: 1.2 g/cm^3

Melting Point: 150-180^{0}C

Properties of PVP:

PVP is soluble in water and other polar solvents. When dry it is a light flaky powder, which readily absorbs up to 40% of its weight in atmospheric water. In solution, it has excellent wetting properties and readily forms films. This makes it good as a coating or an additive to coatings.

Application in Pharmaceutical Formulation:

The cross-linked form of PVP is used as a disintegrant in pharmaceutical tablets. Basically, PVP is a highly cross-linked version of PVP, which makes it insoluble in water but it still absorbs water and swells very rapidly and generates a swelling force. That is why it can be used as a disintegrant in tablets. PVP can be used as a drug, taken as a tablet or suspension to absorb compounds (so-called endotoxins) causing diarrhoea. PVP has E number code E1202 and is used as a stabiliser.

Safety:

The U.S. Food and Drug Administration (FDA) has approved this chemical for many uses, and it is generally considered safe. However, there have been documented cases of allergic reactions to PVP/povidone, particularly regarding subcutaneous (applied under the skin) use and situations where the PVP has come in contact with autologous serum (internal blood fluids) and mucous membranes. For example, a boy having an anaphylactic response after application of PVP-Iodine for treatment of impetigo was found to be allergic to the PVP component of the solution.

7.9. SILICON DIOXIDE:

Synonyms: Aerosil 200, Fumed silica.

Empirical Formula: SiO_2

Density: 2.2 g/cm^3

Specific gravity: 2.2

Melting Point: 1610^0C

Properties:

White, amorphous powder of fumed silica, tasteless, odorless, light density powder, property of swelling in liquid. Primary particle size is 5–50 nm. The particles are non-porous and have a surface area of 50–600 m^2/g.

Production:

Fumed silica is made from flame pyrolysis of silicon tetrachloride or from quartz sand vaporized in a 3000°C electric arc.

Application in Pharmaceutical Formulation:

Fumed silica serves as a universal thickening agent and a anticaking agent (free-flow agent) in powders. Like silica gel, it serves as a desiccant. It is used in cosmetics for its light-diffusing properties. It is used as a light abrasive, in products like toothpaste. Other uses include filler in silicone elastomer and viscosity adjustment in paints, coatings, printing inks, adhesives and unsaturated polyester resins.

6. EXPERIMENTAL INVESTIGATIONS:

6.1 PREPARATION OF MICRONIZED FENOFIBRATE API:

Micronized fenofibrate was prepared by milling the drug in an Alpine 50 AS jet mill operating at 7-8 bar air pressure using a pressurized gas as compressed air and a feed rate of 0.5-1.0g/min. The milled powders were subjected to the following physical and analytical tests.

6.2 PREFORMULATION STUDIES[77]:

- Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with excipients. It is the first step in the rational development of dosage forms.
- The overall objective of preformulation testing is to generate information useful to the formulation in developing stable as well as bioavailable dosage forms.
- The use of preformulation parameters maximizes the changes in formulating an acceptable, safe, efficacious and stable product.
- The drug (Fenofibrate) available in Non-micronised as well as micronized powder form and granules were subjected to the following physical and analytical tests.

6.2.1 I.R SPECTRUM FOR FENOFIBRATE[78]:

FT-IR spectra of prepared melt granules were recorded on Shimadzu FT IR – 8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). The IR spectrum of substances compared with that obtained concomitantly for the corresponding USP reference standard provides perhaps the most conclusive evidence of the identity of the substance. Potassium bromide (KBr) pellet method was carried out. Fenofibrate (micronized and non-microized) and KBr were compressed under 15 tons pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000 to 400cm^{-1} in IR spectrometer.

6.2.2 DRUG – EXCIPIENTS COMPATIBILITY STUDIES:

About 500 mg of micronized fenofibrate alone and mixtures, consisting of micronized fenofibrate with various excipients in 1: 1 and 1: 10 ratio in glass vial were taken and kept at various accelerated condition [25^{o}C / 60% RH, 30^{o}C / 75% RH, 40^{o}C / 75% RH] in stability

chamber. It is carried out for one month in open and closed glass vials. At the interval days of 1, 2, 3, 4, 5, 6, 14, 21 and 30 days samples were withdrawn and physical characteristics like colour change and clumps, if any were recorded. Finally the mixtures with no colour change and no clumps were shown for selected formulations.

PHYSICAL PROPERTIES[79]:

6.2.3 DETERMINATION OF BULK DENSITY AND TAPPED DENSITY:

An accurately weighed quantity of the powder (or) granules (W) were carefully poured into the graduated cylinder and the volume (V_o) was measured. The graduated cylinder was fixed in the density determination apparatus and tapped for 750 times and again subjected to 1250 taps till the constant reading was obtained (V_f). The bulk and tap densities were calculated using the following formulae.

Bulk density = W / V_o

Tapped density = W/V_f

W = weight of the powder; V_o = initial volume; V_f = final volume

6.2.4 DETERMINATION OF HAUSNER RATIO AND CARR'S INDEX:

Hausner ratio and the carr's Index are the measures of interparticle friction and the potential powder arch (or) bridge strength and stability respectively which have been widely used to estimate the flow properties of powders.

Hausner ratio and carr's Index were calculated using the following equation,

$$\textbf{Hausner ratio} = \frac{\rho_{tap}}{\rho_{bulk}}$$

$$\textbf{carr's index} = \frac{\rho_{tap}-\rho_{bulk}}{\rho_{tap}} x100$$

ρ_{tap} = tapped density of powder; ρ_{bulk} = bulk density of powder

6.2.5 DETERMINATION OF ANGLE OF REPOSE :(θ)

The pure drug & granules were subjected to angle of repose by funnel method. The frictional forces in a loose powder can be measured by the angle of repose, θ. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. The angle of repose is calculated by

$$\theta = \tan^{-1}(h/r)$$

θ = angle of repose; h = height of the conical heap; r = radius of the base of the heap.

6.2.6 LOSS ON DRYING:

It was done in Electronic Loss on Drying (LOD) apparatus (Sartorius, Germany). Weighed quantity of 1gm sample was placed in the pan and the temperature was increased to 50^{o}C for 5mins and the loss on drying in percentage was noted.

6.2.7 AQUEOUS SOLUBILITY[80]:

Aqueous solubility was determined using the shaker-flask method. Two grams of neat drug was added to 50 mL of reagent grade water and was shaken for 24 hours at 25°C ± 1°C. Filtered samples were analyzed spectrophotometrically at the wavelength of maximum absorption for Fenofibrate drug. Each sample was analyzed in triplicate.

6.2.8 ANALYTICAL METHODS[81]:

Standard calibration curve of API:

A) Preparation of 0.05M SLS media:

SLS (14.5gm) was accurately weighed and to this distilled water was added to make volume upto 1000ml.

B) Preparation of Stock solution:

Fenofibrate API (50mg) was taken in 100ml standard flask and made up to 100 ml with 0.05M SLS to form primary stock solution. From primary stock solution 2 ml was taken in 100 ml standard flask and made up to 50 ml with 0.05M SLS to a concentration of 20 mcg / ml.

C) Sample solution :

From the secondary stock solution aliquots ranging from 1 to 5 ml were pipetted out and diluted to 10 ml with phosphate buffer to get the concentration of 2, 4, 6, 8, 10 mcg / ml the absorbance was measured at UV Spectrophotometrically 291nm.

A standard graph was plotted by keeping the known concentration on X axis and obtained absorbance on Y axis.

CRYSTAL PROPERTIES[82]:

6.2.9 PARTICLE SIZE DETERMINATION:

The volume mean diameter was measured using low angle laser light scattering. The drug particles were suspended in filtered, deionised water containing 0.05% (w/v) polyoxyethylene sorbitan monooleate and briefly bath sonicated prior to measurements to ensure there was no aggregation.

6.2.10 SURFACE AREA DETERMINATION:

The specific surface area of the Non-micronized and micronized fenofibrate particles was determined using a SA3100 Surface Area. Single-point BET determinations by fenofibrate was degassed at 60°C owing to their melting points being below 100°C. Surface area calculations were made based on the BET equation using the software provided.

6.2.11 MELTING POINT DETERMINATION:

The measurement of melting point involves placing Non-micronized and micronized form of fenofibrate API in melting tube and its placed in the well of an electrical melting point apparatus and observing the melting through the viewer.

6.2.12 X-RAY DIFFRACTION (XRD):

Pulverized mass of Fenofibrate API was used for XRD studies. The samples were studied by using Philips PW3710 X-ray diffractometer. Samples (Non-micronised and micronized Fenofibrate) were irradiated by Cu Kα radiation (1.54 Å) and analyzed between 5 to 40^0. The current and voltage applied were 30mA and 40kV, respectively.

8.3 FORMULATION CHART:

Ingredients (Qty/unit) in mg	Optimiztion of binder concentration			Optimization of sodium lauryl sulfate concentration				Optimization of granulation fluid		
	F01	F02	F03	F04	F05	F06	F07	F08	F09	F10
Dry Mixture										
Fenofibrate	200	200	200	200	200	200	200	200	200	200
Micro crystalline cellulose (Avicel-101)	27	21	15	30	30	30	30	30	30	30
Starch (Unipure –F)	12	12	12	12	12	12	12	12	12	12
Polyplasdone (XL-10)	12	12	12	12	12	12	12	12	12	12
Croscarmellose Sodium (Ac-Di-Sol)	12	12	12	12	12	12	12	12	12	12
Sodium lauryl sulfate	9	9	9	---	**6**	**3**	**4.5**	3	3	3
Binder Preparation										
PVP K-30	**12**	**18**	**24**	18	18	18	18	18	18	18
Sodium lauryl sulfate	---	---	---	**9**	**3**	**6**	**4.5**	6	6	6
Purified water	90	90	90	90	90	90	90	**100**	**80**	**70**
Extra-Granulation										
MCC (Avicel pH-101)	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Polyplasdone (XL-10)	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Aerosil 200	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1
Lubrication										
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Total Qty	300	300	300	300	300	300	300	300	300	300

6.4. EVALUATION OF GRANULES:

6.4.1. DETERMINATION OF PHYSICAL PARAMETERS:

Formulated granules were subjected to Density parameters like Bulk density, Tapped density, Hausner ratio, Compressibility index and angle of repose and Loss on drying was performed as per procedure given above (6.2.3-6).

6.4.2. DETERMINATION OF PARTICLE SIZE DISTRIBUTION:

When the formulated granules were subjected to particle size distribution analysis using sieve shaker, where the different sieve no. like 30, 40, 60, 80, 100 and pan are used to sieve the particles at shaking speed of 50-60 rpm for 5minutes. After sieve shaking calculate the amount of particles are retained on each sieve.

6.4.3. DETERMINATION OF RELATED SUBSTANCE IN GRANULES[83]:

As per ICH as well as USP limit for total impurity of both known and unknown is not more than 1.0%. Related substances were carried out by using suitable method of High performance liquid chromatography technique (Stationary Phase: C18 column, Mobile phase: Acetonitrile : Water : Trifluroaceticacid (700:300:1), Flow rate: 1ml/min. Related substance impurity calculated by using the formula given below.

$$\% \text{ Impurity} = 100 \, (Ai / Ar) \, (Cr / Cu)$$

Ai – Individual impurity peak area;

Ar – Fenofibrate peak area;

Cr – Concentration of fenofibrate formulation;

Cu – Concentration of fenofibrate raw material.

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6.5. EVALUATION OF CAPSULES:

6.5.1. WEIGHT VARIATION TEST:

Individual weight of 20 capsules was taken and average weight for 20 capsules was calculated. The weight variation between capsules was calculated by using the following formula.

Weight variation = [(wt. of individual capsule – Avg. wt.) /Avg. wt. of capsules] ×100

Weight variation should not be more than 7.5% as per USP.

6.5.2. DETERMINATION OF CAP LOCK LENGTH:

Cap lock length was tested by vernier calipers. For the Size.1 capsule range is 19.3± 0.4. Results are compiled in Table No 9.

6.5.3. CONTENT UNIFORMITY TEST:

Standard preparation:

Prepare a solution of Fenofibrate working standard in 0.05M SLS having a known concentration of about 200 ppm.

Sample preparation of Fenofibrate capsules:

Content of twenty capsules was finely taken and dissolved in small amount of methanol shake by mechanical means for 15 minutes, dilute with 0.05M SLS used to get a concentration of 200 ppm and measured the absorbance at 291nm.

6.5.4. DISINTEGRATION TEST:

The disintegration time was measured by using USP disintegration test apparatus. Six capsules were placed in the tubes and the basket was kept in 1-litre beaker of water maintained at 37±2^{0}C. The basket containing capsules move up and down through a distance of 5 to 6cm at a frequency of 28 to 32 cycles per minute. The disintegration time for each capsule is as shown in Table-10.

6.5.5. DISSOLUTION STUDIES[84]:

Release from the capsules was determined in a calibrated USP apparatus 2 (paddle method) in 900ml medium operating at 75rpm and 37^0C. 10ml aliquots were withdrawn at different time intervals of 10, 20, 30, 40, 50 and 60 minutes and it was replaced with equal volume of fresh medium. The withdrawn samples were filtered through 0.45 micron filter and absorbance was measured at 291nm for 0.05M SLS.

6.5.6. SIMILARITY FACTOR (F_2) [85]:

The values of similarity factor (F_2) were used to compare the dissolution profiles of optimized experimental batch and reference. The dissolution profiles so obtained were compared with the purpose of maximizing the chances of success during the bioequivalence tests.

$$f_2 = 50 + \log \{[1+ (1/n) \sum_{t=1} * n (R_t-T_t)^2]^{-0.5} *100\}$$

6.5.7. ANALYSIS OF RELEASE DATA[86]:

To analyze the mechanism of release, the best formulation was subjected to some statistical tests. The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time) and Korsmeyer-Peppas (log cumulative percentage of drug released versus time) equation models.

6.5.8. DSC STUDIES[87]:

For the optimized formulation F10 Differential Scanning Colorimetry analysis were performed to characterize drug – excipients compatibility. DSC curves were obtained by using a DSC-821 (Mettler-toledo, Switzerland), at a heating rate of 5 K//min from 25 to 250^{o}C in a nitrogen atmosphere.

6.5.9. STABILITY STUDIES[88]:

As per *in vitro* release formulation F_{09} was found to be desirable than other formulations. Hence it was chosen for stability studies. The capsules were packed and kept for 3 months at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH in a stability chamber (Osworld, Mumbai). At the interval of 1 month capsules were withdrawn and evaluated for physical properties like cap lock length, weight variation, moisture content and content uniformity. *In vitro* drug release was also carried out.